COMPARATIVE EFFICACY OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR VS CONVENTIONAL EPO THERAPY IN CORRECTING ANEMIA IN PATIENTS ON LONG-TERM HEMODIALYSIS

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Dedicated

to

my Family

&

Teachers

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Success is how high you bounce when you hit bottom.

- George S. Patton

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LIST OF ABBREVIATIONS

CKD	Chronic kidney disease
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
IV	Intravenous
Hb	Hemoglobin
CERA	Continuous erythropoietin receptor activator
rHuEPO	Recombinant human erythropoietin
HLA	Human leukocyte antigen
RBC	Red blood cell
Hct	Hematocrit
WHO	World Health Organization
KDIGO	Kidney Disease: Improving Global Outcomes
eGFR	Estimated glomerular filtration rate
CRP	C-reactive protein
ESKD	End stage kidney disease
HIF	Hypoxia-inducible transcription factor
BFU-e	Burst-forming units erythroid
CFU-e	Colony-forming units erythroid
CHO	Chinese hamster ovary
IP	Intra-peritoneal
SC	Subcutaneous
HD	Hemodialysis
PRCA	Pure red cell aplasia
PEG	Poly-ethylene glycol

CI	Confidence interval
RR	Relative risk
CrCl	Creatinine clearance
BP	Blood pressure
AE	Adverse event
Pg	Picogram
IU	International unit
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
TIW	Thrice every week
QW	Once every week
µg	Microgram
ng	Nanogram
pg	Picogram
ml	Milliliter
dl	Decilitre
SD	Standard deviation
TP	Treatment period
ITT	Intention to treat
PP	Per protocol
DA	Darbepoetin alfa
DMCH	Dayanand Medical College and Hospital
Na	Sodium
K	Potassium
TIBC	Total iron binding capacity

ECG	Electrocardiogram
KDOQI	Kidney Disease Outcome Quality Initiative
TSAT	Transferrin saturation
BMI	Basal metabolic index
HTN	Hypertension
DM	Diabites Mellitus
CAD	Coronary artery disease
CVA	Cardio-vascular accident
CGN	Chronic Glomerulonephritis
GBM	Glomerular basement membrane
ANCA	Anti-neutrophilic cytoplasmic antibody
BPH	Benign prostate hyperplasia
VUR	Vesico-ureteric reflux
CLD	Chronic liver disease
GI	Gastro intestinal
BT	Blood transfusion
IC	Intra-cranial
RRF	Residual renal function
QoL	Quality of life

ABSTRACT

Introduction: Anemia in CKD is caused by a relative deficiency of erythropoietin (EPO). The short half-lives of traditional ESAs may contribute to considerable fluctuations in haemoglobin (Hb) levels, which is seen often in patients with CKD treated with these agents. Continuous erythropoietin receptor activator (CERA) is composed of epoetin beta chemically bound to a linear methoxy-polyethylene glycol moiety hence has an increased half life. This study was conducted to compare the efficacy of IV CERA versus conventional IV epoetin beta in correcting anemia in Indian population on maintenance hemodialysis.

Materials & methods: This was an Open-label, single center, randomized, parallel-group. The Study was of 24 weeks duration (excluding the screening period). After a 2-week screening period, a total of 100 eligible patients were randomized 1:1 in two groups to receive either CERA or epoetin beta. During 24-week study period, dose adjustments were performed to either achieve Hb level of ≥11 g/dL or an increase in Hb of ≥1 g/dL from each patient's baseline Hb. CERA doses were adjusted according to the predefined protocol, but no more often than once every 4 weeks. Patients were evaluated weekly during the screening and every 2 weeks during the 24 weeks study period, and at the final visit. For all patients who recieved at least one dose of study drug, adverse events (AEs) were recorded.

Results: The Hemoglobin response rate was similar in both EPO and CERA groups after 24 weeks correction period. Time to Hemoglobin response was longer in CERA group as Compared to EPO group. Requirement of Blood transfusions were similar in both CERA and EPO groups. Overall Hemoglobin response rates were poorer in diabetic as compared to non-diabetic population in both the groups. Time to Hemoglobin response was similar in diabetic and non-diabetic populations. Higher incidence of worsening of blood pressure was seen in CERA group as compared to EPO group but overall difference in adverse events was insignificant.

Conclusions: Our results show that CERA once every 2 weeks is as effective and well tolerated as more frequent (3 times per week) epoetin with predictable and controlled correction of anemia. Although, time to hemoglobin response was longer in CERA group as compared to EPO group. This must be kept in mind while converting twice per month CERA to once per month maintenance CERA therapy. These features have the potential to provide advancement in the management of anemia by minimizing renal unit workload during the correction of anemia.

Keywords: EPO, CERA, CKD

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INTRODUCTION

Most patients with chronic kidney disease (CKD) develop anemia along with progressive loss of renal function. Anemia is caused by a relative deficiency of erythropoietin (EPO). After recombinant human EPO was introduced in 1989, exogenous replacement of EPO became the standard treatment of anemia in patients with CKD. [1] In patients with CKD on dialysis, treatment of anemia requires life-long replacement with EPOs. Traditional Erythropoiesis stimulating agents (ESAs) have relatively short intravenous (IV) half-lives (epoetin alfa and beta, 7 to 9 hours [2]; darbepoietin alfa, 25 hours [3] and require frequent (up to 3 times weekly) administration.[4,5] The short half-lives of these ESAs also may contribute to considerable fluctuations in haemoglobin (Hb) levels beyond target ranges, which is seen often in patients with CKD treated with these agents.[6-10] Only around 40% of dialysis patients are within Hb level target range (11 to 12 g/dL) at any time, and many move in and out of range over time.

Thus, maintaining stable Hb levels at greater than 11 g/dL requires regular monitoring and often involves frequent ESA dose adjustments, which is time consuming, and labour intensive, a burden that is expected to increase with the predicted increase in CKD prevalence. [11-13]

One approach to address this challenge is the introduction of agents that produce smooth and steady erythropoesis at extended administration intervals and will provide predictable responses across the entire CKD continuum without loss of Hb level stability. Therefore, EPO with extended half-life and sustained efficacy may improve the convenience and therapeutic utility of the drug.

Continuous erythropoietin receptor activator (CERA) is composed of epoetin beta chemically bound to a linear methoxy-polyethylene glycol moiety.[14] In contrast with short-acting EPOs, CERA shows an increased half life, about 130 hrs.[15] The ability to use CERA and conventional

EPOs, with correction or maintenance purposes has been examined in several clinical trials. Among them, there was one phase III correction study which showed comparable efficacy with once every 2 weeks intravenous administration of CERA to that of 3 times weekly epoetin for hemoglobin correction in EPO-naïve patients on dialysis. [16] As this trial contained the patients on the relatively short-term dialysis and small number of Asian patients (less than 10%), there is a lack of evidence of efficacy and safety in general dialysis patients and also in Indian patient population.

This study was conducted to demonstrate the efficacy of CERA treatment for correction of anemia in Indian patients receiving dialysis.

AIMS AND OBJECTIVES

- To compare the efficacy of IV CERA versus conventional IV epoetin beta in correcting anemia in Indian population on maintenance hemodialysis support.

REVIEW OF LITERATURE

Anemia is an almost universal complication of chronic kidney disease (CKD). It contributes considerably to reduced quality of life of patients with CKD and has been associated with a number of adverse clinical outcomes. Before the availability of recombinant human erythropoietin (rHuEPO, or epoetin), patients on dialysis frequently required blood transfusions, exposing them to the risks of iron overload, transmission of viral hepatitis, and human leukocyte antigen (HLA) sensitization, which reduced the chances of successful transplantation.

The advent of rHuEPO in the late 1980s changed this situation completely. There is a strong rationale for managing anemia in CKD patients, and yet the optimal treatment strategies are still incompletely defined. Apart from therapy with erythropoiesis-stimulating agents (ESAs), iron replacement is essential for anemia management.

DEFINITION OF ANEMIA IN CKD

Anemia is a state characterized by a reduced mass of red blood cells (RBCs) and hemoglobin concentration in blood, resulting in reduced oxygen-carrying capacity and delivery to the body's tissues and organs. Because direct measurements of red cell mass are cumbersome and not readily available, anemia is defined as a reduction below the normal range for Hb concentration and hematocrit (Hct); these values depend on gender, race, and age, with an increased prevalence of anemia in older adults. The World Health Organization (WHO) defines anemia as an Hb concentration below 13.0 g/dL for adult men and below 12.0 g/dL for adult women.[17] This definition has been adopted in the clinical practice guideline for anemia in CKD developed by Kidney Disease: Improving Global Outcomes (KDIGO).[18]

EPIDEMIOLOGY

Anemia is more frequent at lower levels of kidney function, becoming almost universal in those with end-stage kidney disease .The prevalence

reported in different studies depends on the definition of anemia and the target population.

A cross sectional study was carried out in Indian CKD patients of all age for a period of two year from Sept 2014 to 2015, at a tertiary care hospital. A total of 408 CKD patients (Mean age: 52.05±12.4Y) were enrolled for study purpose. According to WHO anemia definition, the number of male patients diagnosed with mild, moderate and severe anemia were 26% (N=58), 30% (N=66) and 36% (N=80), respectively. In females the prevalence of mild, moderate and severe were 10% (N=19), 47% (N=89), 22% (N=42). Anemia was found to be most prevalence in CKD V (95%) followed by patients in CKD IV, III and II stages (91%, 85%, 77%, and 68%, respectively). Of all, 87% of the patients were diagnosed with anemia. Combination of vitamin B12+iron+folic acid was found to be most commonly prescribed to 98% of the patients, followed by iron injection, folic acid and erythropoietin injection (17%, 9%, and 11%, respectively). The likelihood of anemia was significantly higher in patients over 60 yrs (OR 1.21, 1.09-2.41; $p<0.05$). [19]

For people with an eGFR of 30 to 59 mL/min/1.73 m2 , low concentrations of 25-hydroxyvitamin D—25(OH)D—and elevations in C-reactive protein (CRP) were independently associated with Hb concentrations below 12 g/dL. A similar association has been described in End stage kidney disease (ESKD) patients who had undergone kidney transplantation. Other studies have also reported an independent association of high-sensitivity CRP results with anemia in patients with an eGFR less than 60 mL/min/m^2.

Anemia develops earlier in the course of CKD in patients with diabetes mellitus, and its magnitude tends to be more severe in patients with diabetes mellitus than in patients without diabetes.

Men with CKD tend to have a higher prevalence of anemia with older age, but among women with CKD, anemia is more frequent at a younger age. It

is likely that the high prevalence of iron deficiency in menstruating women accounts for this difference. [20]

PATHOGENESIS

Renal anemia is typically an isolated normochromic, normocytic anemia with no leukopenia or thrombocytopenia. Both RBC life span and the rate of RBC production are reduced, but the latter is more important. The normal bone marrow has considerable capacity to increase the rate of erythropoiesis, and compensation normally could be easily made for the reduction in erythrocyte life observed in association with CKD. However, this EPO-induced compensatory increase in erythrocyte production is impaired in CKD. Serum EPO levels remain within the normal range and fail to show the inverse exponential relationship with blood oxygen content characteristic of other types of anemia. EPO is normally produced by interstitial fibroblasts in the renal cortex, in close proximity to tubular epithelial cells and peritubular capillaries. [21,22] In addition, hepatocytes and perisinusoidal, cells in the liver can produce EPO. Hepatic EPO production dominates during fetal and early postnatal life but does not compensate for the loss of renal production in adult organisms. Subtle changes in blood oxygen content induced by anemia, reduced environmental oxygen concentrations, and high altitude stimulate the secretion of EPO through a widespread system of oxygen-dependent gene expression.[22-24] Central to this process is a family of hypoxia-inducible transcription factors (HIFs). The two most important members of this family, HIF-1 and HIF-2, are composed of an oxygen-regulated α subunit (HIF-1α or HIF-2α) and a constitutive β subunit. The production of HIF-1α and HIF-2α is largely independent of oxygen, but their degradation is related to cellular oxygen concentrations. Hydroxylation of specific prolyl and asparagyl residues of HIF-α, for which molecular oxygen is required as a substrate, determines proteasomal destruction of HIF and inhibits its transcriptional activity. Apart from EPO, several hundred HIF target genes have been identified. HIF-2, rather than HIF-1, is the transcription factor

primarily responsible for the regulation of EPO production. [25.26] The role of renal EPO production in the pathogenesis of renal anemia is supported by the particularly severe anemia in anephric individuals. However, the mechanisms impairing renal EPO production in diseased kidneys remain poorly understood. The production capacity for EPO remains significant, even in end-stage renal disease. Thus patients with anemia and CKD can respond with a significant increase in EPO production to an additional hypoxic stimulus. [21] The main problem therefore appears to be a failure of EPO production to increase in response to chronically reduced hemoglobin concentrations. In line with this view, endogenous EPO production can be induced in CKD patients by pharmacologic inhibition of HIF degradation. EPO is a glycoprotein hormone consisting of a 165–amino acid protein backbone and four complex, heavily sialylated carbohydrate chains. [21] The latter are essential for the biologic activity of EPO in vivo because partially or completely deglycosylated EPO is rapidly cleared from the circulation. This is why rHuEPO has to be manufactured in mammalian cells; bacteria lack the capacity to glycosylate recombinant proteins. EPO stimulates RBC production by binding to homodimeric EPO receptors, which are primarily located on early erythroid progenitor cells, the burst-forming units erythroid (BFU-e) and the colony-forming units erythroid (CFU-e). Binding of EPO to its receptors salvages these progenitor cells and the subsequent earliest erythroblast generation from apoptosis, thereby permitting cell division and maturation into RBCs. [27] Inhibition of RBC production by yet unknown uremic inhibitors of erythropoiesis may contribute to the pathogenesis of renal anemia, and dialysis per se can improve renal anemia and the efficacy of ESAs. Moreover, the inter-individual dose requirements for ESAs vary significantly among CKD patients, and the average weekly dose is much higher than estimated production rates of endogenous EPO in healthy individuals. An alternative view to the accumulation of inhibitors of erythropoiesis in CKD is that in many patients there is overlap between

renal anemia and the anemia of chronic disease, which is characterized by inhibition of EPO production and EPO efficacy, as well as by reduced iron availability, mediated through inflammatory cytokines.[28] The hepatic release of hepcidin, the key regulator of iron metabolism, is upregulated in states of inflammation; it simultaneously blocks iron absorption from the gut and promotes iron sequestration in macrophages.[29]

Epoetin Therapy

In 1905, Paul Carnot proposed the idea that a hormone regulates the production of red blood cells. After conducting experiments on rabbits subject to bloodletting, Carnot and his graduate student Clotilde-Camille Deflandre attributed an increase in red blood cells in rabbit subjects to a hemotropic factor called hemopoietin. [30] Eva Bonsdorff and Eeva Jalavisto called the hemopoietic substance 'erythropoietin'.

K.R.Reissman and Allan J. Erslev demonstrated that a certain substance, when circulated in the blood, is able to stimulate red blood cell production and increase hematocrit. He infused 100 to 200 mL of plasma from bled anemic rabbits into normal rabbit recipients. The reticulocyte count increased rapidly, with a fourfold increase in cell count within 4 days of infusion. [31,32]

In 1957, Jacobson and coworkers provided indirect evidence to suggest that the kidneys were the primary source of EPO. After demonstrating that removal of a variety of different organs did not affect EPO production after phlebotomy, they showed that nephrectomized rats and rabbits failed to increase EPO production after blood loss.[33] Further studies by Koury and Lacombe and associates have demonstrated that the cells responsible for EPO production are peritubular interstitial cells,[34,35] which were subsequently identified as peritubular fibroblasts, located in the renal cortex.[36] Although the nature of these cells has still not been fully clarified, they have been suggested to be derived from the neural crest and share characteristics of pericytes.[37,38]

In 1977, Goldwasser and Kung purified EPO.[39] Pure EPO allowed the amino acid sequence to be partially identified and the gene to be isolated.

In 1985, Lin *et al* isolated the human erythropoietin gene from a genomic phage library and used it to produce EPO.[40]

Synthetic EPO was first successfully used to correct anemia in 1987.[41] In 1989, the US Food and Drug Administration approved the hormone Epogen for use in certain anemias.

Gregg L. Semenza and Peter J. Ratcliffe studied the EPO gene and its oxygen-dependent regulation. Along with William Kaelin Jr., they were awarded the 2019 Nobel Prize in Physiology or Medicine for their discovery of hypoxia-inducible factor , which regulates the EPO gene, as well as other genes, in response to hypoxia.[42]

The term epoetin is usually applied to rhEPO preparations, produced by means of over expression of the human EPO gene in mammalian cell lines. Production in mammalian cells rather than bacteria is required because EPO is a highly glycosylated molecule, and bacteria lack the ability to generate glycoproteins. Manufacture of rHuEPO is achieved by gene transfer into a suitable mammalian cell line such as Chinese hamster ovary (CHO) cells. Like the endogenous hormone, rHuEPO consists of a 165–amino acid backbone with one *O*-linked and three *N*-linked glycosylation chains. Epoetin alfa and epoetin beta are the two compounds first developed by two different companies. Both are produced in Chinese hamster ovary cells and show a high degree of similarity, with identical protein backbones of 165 amino acids and one O-linked and three N-linked glycosylation sites each, but with subtle differences in their carbohydrate composition.[43]

Although the amino acid sequence unequivocally determines glycosylation sites, the precise composition of the sugar side chains is also determined by the repertoire and activity of glycating enzymes, which may vary among cell lines and under different tissue culture conditions. Glycosylation of the EPO molecule is not required for binding or activation of its receptor; in

fact, the in vitro activity of deglycosylated erythropoietin is enhanced.[44] However, in vivo deglycosylated EPO is inactive because of rapid clearance from the circulation, and the carbohydrate chains are thus responsible for its pharmacokinetic properties.

Early clinical trials in patients on hemodialysis used IV epoetin administered three times weekly; subsequently, the intraperitoneal (IP), subcutaneous (SC), and intradermal routes of administration were also investigated.[45,46] After IV administration, plasma EPO concentrations decay mono-exponentially, with an elimination half-life of approximately 4 to 11 hours. The apparent volume of distribution of EPO is about one to two times the plasma volume, and the total body clearance is lower than for other protein hormones, such as insulin, glucagon, and prolactin. The IP route was investigated as a potential means of administering EPO to patients on peritoneal dialysis but the bioavailability of intraperitoneal epoetin is disappointingly low, 3% to 8%. This application has therefore not been pursued.[45]

With SC administration, peak serum concentrations of about 4% to 10% of an equivalent IV dose are obtained at around 12 hours, and thereafter they decay slowly, so that concentrations greater than baseline are still present at 4 days.[46,47] The bioavailability of SC epoetin is around 20% to 25%. Nevertheless, SC application is even more efficient than IV application, allowing a dose reduction of approximately 30% to maintain the same hemoglobin concentration.[48,49]

Presumably, the early peak concentrations of epoetin after IV injection are inefficient, and the more prolonged elevation of hormone levels following SC application allows a more sustained stimulation of RBC production. Thrice-weekly administration has remained the most popular dosage frequency for both IV and SC administration, although once weekly[50], twice-weekly, and seven times weekly (once-daily) dosing have all been used.[51] With IV epoetin, once-weekly administration is associated with much lower efficacy, and twice- or thrice-weekly dosing is required. In

2015, the mean weekly dose of EPO in adult hemodialysis (HD) and peritoneal dialysis patients in the United States was below 10,000 U/week, a substantial reduction when compared with 2010 values. A number of additional epoetin preparations have been developed worldwide. Some have distinct differences in the production process—for example, epoetin delta was produced in a human cell line through increased transcription of the endogenous EPO gene[52], but this product is currently not being distributed. Other epoetins are so-called “biosimilar” generic drugs designed as copies of epoetin alfa or beta; these are being licensed on the basis of a more limited clinical trial program after expiration of the patents for the originator compounds in Europe.

The importance of the formulation of epoetins was highlighted in 2002 with an upsurge in cases of antibody-mediated, pure red cell aplasia (PRCA) in association with the SC use of epoetin alfa marketed outside the United States after a change to an albumin-free formulation. Patients affected by this complication develop neutralizing antibodies against both rhEPO and the endogenous hormone, resulting in severe anemia and transfusion dependence.[53] The cause of this serious complication remains obscure, although circumstantial evidence suggested that rubber stoppers of prefilled syringes used for the albumin-free epoetin alfa formulation may have released organic compounds that act as immunologic adjuvants.[54] Factors such as breach of the cold storage chain may also have played a role. In anti-EPO antibody cases observed so far, the SC application route was usually a prerequisite. Although the unfortunate combination of adverse factors leading to a temporary increase in antibody induced PRCA was specific for one product, a low baseline rate of PRCA also occurs with use of epoetin beta and darbepoetin alfa .

Methoxypolyethylene Glycol Epoetin Beta

Alternative bioengineering techniques to prolong the half-life of EPO further have resulted in the development of methoxypolyethylene glycol

epoetin beta (also called “continuous erythropoietin receptor activator” [CERA]), a PEGylated derivative of epoetin beta with an elimination half-life of about 130 hours when administered IV or SC.[55-57] A methoxypolyethylene glycol polymer chain is integrated through amide bonds between the N-terminal amino group or the ε-amino group of lysine (predominantly lysine-52 or lysine-45), with a single succinimidyl butanoic acid linker. The molecular weight of CERA is twice that of epoetin (~60 kDa).

Phase III studies have shown that because of the longer half-life time of CERA, less frequent injections are sufficient to maintain stable hemoglobin values CERA given IV once every 2 weeks was found to be as safe and effective as epoetin given thrice weekly for correcting anemia in patients on hemodialysis.[16] Conversion factors have been established and tested for switching from other ESAs to CERA.[58] The usual intravenous or subcutaneous starting dose of epoetin is about 25 to 50 IU/kg (e.g., 2000 IU two or three times weekly), of darbepoetin alfa is 20 to 30 mcg once weekly, and of CERA is 30 to 60 mcg once every 2 weeks. Within 3 to 4 days after treatment initiation, an increase in the reticulocyte count is seen, and within 1 to 2 weeks, there is a significant rise in the Hb concentration, usually of the order of 0.25 to 0.5 g/dl/wk. Thus, over the course of 1 month, a significant increase of 1 to 2 g/dl in Hb concentration is usually achieved. If a patient fails to respond satisfactorily to ESAs, the dose is increased in stepwise upward titrations of 25% to 50%, and if there is still an inadequate response, causes of resistance to ESA therapy should be investigated

In a Cochrane database review, 27 studies involving 5410 adults with CKD were included. Seven studies (1273 participants) involved people not requiring dialysis, 19 studies (4209 participants) involved people treated with dialysis and one study (71 participants) evaluated treatment in recipients of a kidney transplant. Treatment was given for 24 weeks on average. One study compared CERA with placebo, nine studies CERA

with epoetin alfa or beta, nine studies CERA with darbepoetin alfa, and two studies compared CERA with epoetin alfa or beta and darbepoetin alfa. Three studies assessed the effects of differing frequencies of CERA administration and five assessed differing CERA doses. There was low certainty evidence that CERA had little or no effects on mortality (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65), major adverse cardiovascular events (RR 5.09, 95% CI 0.25 to 105.23; RR 5.56, 95% CI 0.99 to 31.30), hypertension (RR 1.01, 95% CI 0.75 to 1.37; RR 1.00, 95% CI 0.79 to 1.28), need for blood transfusion (RR 1.02, 95% CI 0.72 to 1.46; RR 0.94, 95% CI 0.55 to 1.61), or additional iron therapy (RR 1.03, 95% CI 0.91 to 1.15; RR 0.99, 95% CI 0.95 to 1.03) compared to epoetin alfa/beta or darbepoetin alfa respectively.[59]

Sameer G. Vankar et al conducted a prospective, open-labelled, pilot clinical study in 35 adult type 2 diabetes patients with nephropathy and renal anaemia, who were not on dialysis nor receiving treatment with ESA. All were administered CERA subcutaneously once in two weeks for a period of 24 weeks. All patients showed Hb rise ≥1 g/dl during the study period and 80 per cent patients could achieve Hb value ≥11 g/dl. The maximum median Hb rise of 1.2 g/dl occurred in the initial 6 weeks after starting the treatment. The mean creatinine clearance (CrCl) improved by 2.8 ml/min, with mean Hb rise of 2.6 g/dl from the baseline after administration of CERA. Worsening of blood pressure (BP) control (42.9%) was the most common adverse event. Concluding that CERA once in two weeks was efficacious in correcting anaemia in the ESA-naïve patients with diabetic nephropathy who are not on dialysis.[60]

Thomas Weinreich et al conducted a prospective, multicenter, non-interventional trial with a duration of up to 9 months (month 0-5 "titration phase"; month 6-8 "evaluation phase") to test the stability of Hb control in hemodialysis patients under routine conditions. Patient selection, Hb targets and CERA dosing were at the discretion of the local nephrologist. 918 patients from 92 German nephrology centers were included. Ninety-

three percent were on ESA treatment prior to study entry. The mean number of CERA dose changes during the study was 1.9 ± 1.9 per patient. Mean Hb level was 11.4 ± 1.2 g/dL at baseline and 11.7 ± 1.4 g/dL at the end of the 8-month study. During the evaluation phase (months 6-8), 15.6%, 40.3%, and 66.0% of patients had stable Hb (i.e., at least two values) in the ranges 11-12, 10-12, and 10-13 g/dL, respectively. The mean intra-individual fluctuation in Hb was 1.4 ± 0.7 g/dL during the study (0.5 ± 0.4 g/dL during the 3-month evaluation phase). More than 90% of patients, and > 80% of physicians, rated CERA therapy as "very good" or "good" throughout the study. Four patients (0.4%) discontinued prematurely due to adverse drug reactions. Hence, concluding that once-monthly CERA therapy maintained stable Hb values with low intra-individual variability and few dose adaptations in hemodialysis patients when administered entirely according to local practice, and the regimen was well-tolerated.[61]

Francesco Locatelli et al conducted a Phase II, randomized, multicentre, open label study aimed to determine the optimal dose and administration schedule of continuous erythropoietin receptor activator (CERA) given subcutaneously in patients receiving dialysis converting directly from subcutaneous epoetin therapy 1-3 times/week. 137 patients entered the core period, and 62 continued into the extension period. A dose-dependent relationship was seen in the primary efficacy variable, change in Hb standardized to a 6 week period ($p < 0.0001$), but effect was independent of schedule. Hb levels were maintained throughout the study, with few dose changes. CERA was generally well tolerated and the most frequent adverse event was hypotension.

The results suggest that subcutaneous CERA at up to once monthly intervals provides stable maintenance of Hb levels in dialysis patients converting directly from epoetin 1-3 times/week. Achieving tight Hb control with few dose adjustments at extended administration intervals may offer health benefits and improvements in resource management.[62]

A L M de Francisco et al conducted a dose-finding, open-label study examining the potential of subcutaneous Continuous Erythropoietin Receptor Activator (CERA) to correct anemia at extended administration intervals in 61 erythropoiesis-stimulating agent-naïve patients with chronic kidney disease (CKD) on dialysis. After a 4-week run-in, patients were randomised to CERA 0.15, 0.30 and 0.45 microgram/kg/week. Within these dose groups, patients were further randomised to once weekly, once every 2 weeks or once every 3 weeks treatment. Mean changes in haemoglobin increased with increasing CERA dose during a period of 6 weeks where no dose adjustments were permitted. The effect was independent of administration schedule. Erythropoietic responses were sustained until the end of the study (12 weeks) in all groups. In total, 90% of patients in the 0.30 microgram/kg/week group and 79% in the 0.45 microgram/kg/week group responded to treatment (Hb increase > or =1.0 g/dl), compared with 72% in the 0.15 microgram/kg/week group. Faster median response time was associated with increasing dose (51, 38 and 31 days, respectively) and response was unrelated to administration frequency. CERA was generally well tolerated. Our results suggest that 0.60 microgram/kg twice monthly would be a suitable starting dose of CERA for the initiation of anemia correction in patients with CKD on dialysis.[63]

Anatole Besarab et al conducted a randomized, open-label, dose-finding study at 14 study centers across the United States. Male and female patients aged >/=18 years with CKD and CKD-related anemia and receiving treatment with IV epoetin alfa were enrolled. After a 2-week run-in period in which all patients continued to receive their previous epoetin treatment thrice weekly, patients were switched to CERA at 1 of 3 doses, determined by multiplying the previous weekly epoetin dose by 1 of 3 ratios (0.25 pg/150 IU, 0.4 pg/150 IU, or 0.6 pg/150 IU). Within each dose group, patients were randomized to 1 of 2 frequency subgroups: Once per week or once in two weeks. Dose adjustments were not permitted during

the first 6 weeks; the total dose during this period was the same for a particular dose group across the frequency subgroups. The primary efficacy parameter was change in hemoglobin (Hb) standardized to a 6-week period between baseline and the point when the patient had a dose change or blood transfusion, thus providing an estimate of Hb change based on starting dose. Following completion of a 19-week core period, patients could enter the 12-month extension period, aiming to maintain Hb concentrations between 11 and 12 g/dL.

A total of 91 patients entered the core period (mean age, 58 years; 66% male); 10 patients withdrew prematurely during this period (4 owing to AEs and 6 for other reasons). Fifty-three patients continued into the extension period; 22 patients withdrew during this period (6 because of AEs, and 16 for other reasons). There was a significant dose-response effect ($P < 0.001$) and a significant effect of schedule ($P < 0.002$) for the primary efficacy end point. Stable Hb concentrations were maintained throughout the study (11-12 g/dL, with a narrow 95% CI). No significant difference between schedules was observed during the extension period, and few dose changes were required (mean, 4 and 2 per patient per year in the once weekly and twice weekly groups, respectively). Nineteen and 22 patients experienced serious AEs during the core and extension periods, respectively, but only 1 event was considered related to study treatment. The most frequent AEs were headache and vomiting during the core study period and dizziness, fatigue, chest pain, and pyrexia during the extension period.[64]

In this study, CERA provided effective maintenance of Hb concentrations in patients receiving dialysis treatment who were switched directly from epoetin alfa thrice weekly to CERA once weekly or once in two weeks. CERA was generally well tolerated.

Nathan W Levin et al conducted a open-label, parallel-group, non-inferiority trial, aimed to compare the effectiveness of methoxy polyethylene glycol-epoetin beta, given intravenously at 2-week or 4-week

intervals, with epoetin treatment one to three times per week for haemoglobin control in haemodialysis patients. They established baseline haemoglobin concentration and eligibility over a 4-week run-in period. 223 patients were randomly assigned to receive methoxy polyethylene glycol-epoetin beta every 2 weeks, and 224 to receive it every 4 weeks. The initial dose was based on the average epoetin dose given during the week before the switch. The primary endpoint was change in haemoglobin concentration between baseline and the assessment period. The mean change from baseline haemoglobin for patients who had switched to intravenous methoxy polyethylene glycol-epoetin beta every 2 weeks (-0.71 g/L, 95% CI -2.20 to 0.77) or every 4 weeks (-0.25 g/L, -1.79 to 1.29) was non-inferior to the mean change for patients who continued treatment with epoetin (-0.75 g/L, -2.26 to 0.75) ($p<0.0001$ for both comparisons). Of the 666 patients who received at least one dose of study drug, the incidence of adverse events or serious adverse events did not differ between groups ($p=0.30$ and $p=0.40$, respectively). Hence, concluding that CERA is as safe as conventional epoetin treatment, and can maintain anaemia management in haemodialysis patients when given intravenously at 4-week dosing intervals.[65]

Wladyslaw Sulowicz et al conducted three-arm, comparator-controlled, open-label, randomized, parallel-group, Phase III study, 572 dialysis patients (> or =18 yr) who were receiving stable subcutaneous epoetin one to three times weekly were randomly assigned (1:1:1) to continue epoetin or to receive subcutaneous CERA once monthly or twice monthly for 52 wk. Dosage was adjusted to maintain Hb +/-1.0 g/dl of baseline level. Primary end point was mean change in Hb level between baseline and the evaluation period (weeks 29 to 36). Mean Hb levels during the evaluation period were similar between groups (once-monthly CERA 11.5 g/dl; twice-monthly CERA 11.7 g/dl; epoetin 11.5 g/dl). The difference between CERA and epoetin in mean change (97.5% confidence interval) in Hb concentration between baseline and evaluation was -0.022 g/dl (-

0.262 to 0.217) for once monthly and 0.141 g/dl (-0.098 to 0.380) for twice monthly. Analysis demonstrated that CERA was as effective as epoetin in maintaining Hb and was well tolerated. This study concluded that Subcutaneous CERA once or twice monthly successfully maintained tight and stable Hb levels in patients who were on dialysis and randomly converted directly from epoetin one to three times weekly.[66]

D Fliser et al conducted a prospective, open-label, single-arm, multicentre study performed at 90 nephrology centres in Germany. After a 2-month screening phase, haemodialysis patients receiving epoetin or darbepoetin were converted to monthly intravenous CERA, with a 5-month titration phase followed by a 2-month evaluation phase. The primary efficacy variable, haemoglobin within 11-12.5 g/dL or 10-13 g/dL during the evaluation phase, was achieved in 109 (30.8%) and 265 (74.9%) of the 354 evaluable patients, respectively, with no differences observed between patients formerly receiving epoetin or darbepoetin or different dosing frequencies. During the screening, titration and evaluation phases, mean haemoglobin was 11.7 +/- 0.7 g/dL, 11.6 +/- 0.9 g/dL and 11.4 +/- 1.0 g/dL, respectively, and 90.6% (377/416), 70.4% (293/416) and 82.9% (345/416) of patients exhibited < or = 1 g/dL change from phase-specific individual means. CERA was well-tolerated with a safety profile similar to that reported in phase III studies. In this single-arm, open-label, multicentre study, conversion of a large population of haemodialysis patients from epoetin or darbepoetin to monthly CERA administration using pre-filled syringes was shown to be practical, convenient and offer good control of haemoglobin levels, regardless of the previous type of therapy or dosing frequency.[67]

J F E Mann et al analyzed data from three Phase III maintenance trials, using almost identical protocols, in dialysis patients treated with CERA every 2 weeks (Q2W) or every 4 weeks (Q4W) or a comparator ESA (epoetin or darbepoetin alpha; at their previous dose/administration interval). Dosage was adjusted to maintain Hb ± 1 g/dl of baseline and 10

- 13.5 g/dl during titration (28 weeks) and evaluation (8 weeks), and 11 - 13 g/dl during follow-up (16 weeks). Data were analyzed from 564 patients treated with CERA Q2W, 410 with CERA Q4W and 572 with comparator ESA at their usual dosing interval. Significantly fewer dose changes were needed in patients receiving CERA Q2W ($p < 0.05$) or CERA Q4W ($p < 0.001$) than in patients treated with comparator ESAs.[68] This retrospective analysis suggested that CERA Q4W maintains Hb levels in dialysis patients and requires fewer dose changes compared with other ESAs.

Bruce Spinowitz et al did an open-label, randomized, parallel-group, multicenter Phase III study to determine whether SC or IV CERA (administered in pre-filled syringes) Q2W was as effective and well tolerated as epoetin alfa or epoetin beta QW–TIW for the maintenance treatment of anemia in patients with CKD on dialysis who had been previously treated with epoetin alfa or epoetin beta.Patients (n = 336) were randomized 1:1 to continue epoetin at their current dose, route and administration interval (once to three times weekly (QW-TIW)), or receive CERA Q2W by the same route as previous epoetin treatment for 36 weeks. Dosage was adjusted to maintain patients' Hb within +/-1.0 g/dl of baseline value and within 10.0-13.5 g/dl. Primary endpoint was mean change in Hb between baseline and the evaluation period (weeks 29-36). Mean change in Hb for CERA and epoetin was 0.088 and -0.030 g/dl, respectively (endpoint Hb 11.93 and 11.86 g/dl, respectively). Analysis showed that CERA was as effective as epoetin in maintaining Hb ($p < 0.0001$), and was well tolerate and the administration route had no impact on primary endpoint.[69]

Bernard Canaud et al conducted a multicentre, open-label randomized phase III study to evaluate the efficacy and safety of intravenous CERA administered once every 2 weeks (Q2W) for Hb maintenance following direct conversion from darbepoetin alfa (DA). Adult patients on dialysis receiving stable intravenous DA once weekly (QW) or Q2W were

randomized (1:1) to continue their current DA regimen (n = 156) or receive intravenous CERA Q2W (n = 157) for 52 weeks. Doses were adjusted to maintain Hb levels within +/- 1.0 g/dl of baseline and between 10.0 and 13.5 g/dl. The primary endpoint was the mean Hb change between baseline and the evaluation period (weeks 29-36). Most patients (>80%) received DA QW before randomization. The mean (95% CI) difference between CERA and DA in the primary endpoint was 0.18 g/dl (-0.05, 0.41), within a pre-defined non-inferiority limit. CERA was clinically non-inferior to DA (P < 0.0001) in maintaining Hb levels. Both treatments were well tolerated. This study concluded that Stable Hb levels were successfully maintained in patients on haemodialysis directly converted to Q2W intravenous CERA from DA.[70]

Toru Kawai et al undertook a single-center observational study of 33 Japanese maintenance dialysis patients, whose anemia had been kept stable through weekly administration (QW) of darbepoetin (DA), to evaluate the effectiveness of CERA Q2W switched from DA in maintaining hemoglobin (Hb) levels over a 12-month period. The target Hb level was 10.0-12.0 g/dL. Throughout the 12-month period, the mean Hb was stably maintained at 10.5-10.8 g/dL, 69.7-87.9% of the patients achieving the target Hb level. The mean CERA dose was within the range of 62.9-78.8 µg/2 weeks. The average CERA dose adjustment frequency after switching was low at 0.42-0.67 times/3 months. In both subgroups stratified by the DA dose prior to the switch, Hb levels were kept stable during CERA administration; however, in the low-dose group (10-20 µg/week of DA), the CERA and iron doses decreased over time, whereas in the high-dose group (30-60 µg/week of DA) they remained unchanged. CERA Q2W achieved long-term successful anemia management in Japanese maintenance dialysis patients after switching from DA QW. CERA dose was adjusted based on an overall consideration of past changes in Hb levels, erythropoiesis-stimulating agent and iron doses. Subgroup analysis showed the CERA dose in the low-dose group

decreased continuously, due possibly to a long-term improvement in iron use efficiency.[71]

Marian Klinger et al conducted Open-label, multicenter, randomized, parallel-group, phase 3 study in dialysis patients (n = 181)who were randomly assigned (3:1) to receive intravenous CERA once every 2 weeks or epoetin 3 times weekly. The primary end point was Hb level response rate (increase in Hb level >or= 1 g/dL [10 g/L] versus baseline and Hb level >or= 11 g/dL [110 g/L] without blood transfusion during the 24-week correction period) in the intent-to-treat population. Hb response rates (intent-to-treat population) were 93.3% with CERA and 91.3% with epoetin. Peak mean Hb levels were 12.28 +/- 1.13 (SD) g/dL (122.8 +/- 11.3 g/L) with CERA and 12.19 +/- 1.24 g/dL (121.9 +/- 12.4 g/L) with epoetin. Mean change in Hb levels from baseline to the end of the correction period were 2.70 +/- 1.45 g/dL (27 +/- 14.5 g/L) with CERA and 2.56 +/- 1.31 g/dL (25.6 +/- 13.1 g/L) with epoetin. Both treatments were generally well tolerated. In conclusion, Intravenous CERA once every 2 weeks may be as safe and effective as 3-times-weekly epoetin for correcting anemia in dialysis patients.[16]

Jieun Oh et al conducted a multi-center, phase III, open-label, randomized, prospective study with Patients (≥18 yr) who were not receiving any ESAs for more than 8 weeks being randomly assigned to either intravenous CERA once every 2 weeks (n=39) or epoetin beta thrice-weekly (n=41) during a 24-week correction phase. Hemoglobin (Hb) response was defined as increase of Hb by at least 1 g/dL and Hb≥11 g/dL without red blood cell (RBC) transfusion. Median dialysis duration was 1.7 (0.3-20.8) and 1.6 (0.4-13.8) yr in CERA and epoetin beta group, respectively. Hemoglobin response rate of CERA was 79.5% (95% confidence interval [CI], 63.5-90.7). As the lower limit of 95% CI was higher than pre-specified 60% response rate, it was concluded that CERA corrected anemia (P<0.05). Hb response rate of epoetin beta was 87.8%

(95% CI, 73.8-95.9) (*P*=0.37). Median time to response was 12 weeks in CERA and 10.3 weeks in epoetin beta (*P*=0.03).[72]

It was hence suggested that once every 2 weeks administration of CERA is effective for correcting anemia in Korean patients on long-term hemodialysis with longer time-to-response than thrice weekly epoetin beta.

Georgy K Nainan et al conducted an open label, single arm, prospective, multi-centre study. He included 189 patients on dialysis, having Haemoglobin (Hb) between 8 – 10 g/dL and not receiving any ESA for last 8 weeks from 14 dialysis centers across India. CERA was given intravenous (IV) at the dose of 0.6 µg/kg every two weeks. Primary end point of the study was mean change in Hb concentration from baseline to end of the treatment period (TP) of 16 weeks. Mean change of Hb from baseline to end of TP was 2.11 ± 1.37 g/dL and 2.08 ± 1.29 g/dL in intent to treat (ITT) and per protocol (PP) population respectively. Mean time to achieve Hb response was 6.10 ± 3.87 weeks and 6.16 ± 3.92 weeks in ITT and PP populations respectively. This study concluded that CERA administered once in two weeks in dialysis patients effectively corrected chronic kidney disease (CKD) related anaemia and was well tolerated with no significant untoward effect directly related to drug therapy in Indian population.[73]

MATERIALS AND METHODS

This study was conducted in patients undergoing maintenance hemodialysis at DMCH Dialysis centre from May 2020– May 2021. The study population was followed up for duration of the study i.e 24 weeks (till Oct 2021)

Study Design:

Open-label, single center, randomized, parallel-group study

Source of Data

The study population was enrolled from patients undergoing maintenance hemodialysis in DMCH Dialysis centre from the period of May 2020 to May 2021.

Methods of collection of Data

After an informed consent, enrolled patients in this study were subjected to relevant history taking, physical examination and investigations .A predefined and well-structured performa was used to collect the whole data.

BASELINE INVESTIGATIONS

a) Complete Hemogram, including Peripheral blood film
b) Serum creatinine, urea & serum Na/K
c) Serum iron
d) TIBC
e) Serum Ferritin
f) Reticulocyte count
g) Serum B12
h) Serum folate
i) Serum CRP quantitative
j) anti-EPO antibody (wherever indicated)
k) ECG

l) 2D Echo

m) Kt/v

TREATMENT PROTOCOL

The Study was of 24 weeks duration (excluding the screening period). After a 2-week screening period, a total of 100 eligible patients were randomized 1:1 in two groups to receive either CERA or epoetin beta, according to computer generated randomization list. The starting dose was 0.6 µg/kg of CERA IV once every 2 weeks. The starting dose of epoetin beta was 40 IU/kg IV, three times per week. During 24-week study period, dose adjustments were performed to achieve Hb level ≥11 g/dL or an increase of ≥1 g/dL from each patient's baseline Hb. CERA doses were adjusted according to the predefined protocol, but no more often than once every 4 weeks.

The predefined protocol was as follows;

1) if the Hb increased by <1 g/dL during 4 weeks compared with baseline, doses were increased by 25%;

2) if Hb increased by >2 g/dL versus baseline or was between 12 g/dL and 13 g/dL, doses were decreased by 25%;

3) if Hb was greater than 13 g/dL, then CERA was stopped temporarily until Hb level decreased to less than 12 g/dL, then therapy was resumed at a dose 25% below the previously administered dose;

4) if Hb decreased to less than baseline value and was less than 9 g/dL, doses were increased by 50%.

Dose adjustments of conventional epoetin were performed according to each investigator's discretion, but not more often than once every 4 weeks.

100mg IV iron supplementation was prescribed once weekly to prevent iron deficiency during treatment period. Additional supplementation was done if need be to maintain iron indices (serum ferritin≥500 ng/mL or transferrin saturation (TSAT) ≥30% .

Assessment

Patients were evaluated weekly during the screening and once every 2 weeks during the 24 weeks study period, and at the final visit. Hemoglobin, hematocrit, blood pressure and heart rate were measured at every visit. Iron and other safety laboratory parameters were measured during screening, and every 6 weeks during the study and at the final visit. For all patients who received at least one dose of study drug, adverse events (AEs) were recorded. RBC transfusions, iron supplementation, and concomitant medications were also recorded throughout the study.

PRIMARY END POINT

The primary efficacy parameter was Hb response rate in the intention-to-treat (ITT) population. Hb response was defined as increase of Hb by at least 1 g/dL compared with baseline and Hb ≥11 g/dL without red blood cell (RBC) transfusion during 24-week correction period.

SECONDARY END POINTS

Secondary efficacy parameters were;

1) Mean hemoglobin levels and their changes over time from baseline,
2) Time to Hb response, and
3) RBC transfusion rate during 24-week correction period.

INCLUSION CRITERIA:

1. Patients (age ≥18 yr) receiving regular minimum twice weekly dialysis at least for 4 weeks before randomization.
2. Patients should be on adequate dialysis, that is, measured Kt/V ≥1.2 or urea reduction ratio (URR) ≥65% for hemodialysis (HD).
3. We defined baseline pre-dialysis hemoglobin as mean of all values recorded between the day of first study dose and the previous 20 days. It must be between 8 and 11 g/dL.
4. Patients were also required to have adequate iron status, defined as serum ferritin ≥500 ng/mL or transferrin saturation (TSAT) ≥30%.

EXCLUSION CRITERIA:

1. New York Heart Association class III or IV congestive heart failure
2. Uncontrolled hypertension (defined as predialysis diastolic blood pressure [BP] ≥105 mmHg or systolic BP ≥160 mmHg during the screening period)
3. Evidence of uncontrolled hyperparathyroidism (defined as parathyroid hormone level >1000 pg/mL with no response to conventional treatment of hyperparathyroidism according to KDOQI guideline during the 12 months prior to baseline)
4. Treatment for grand mal epilepsy
5. Haematological, inflammatory, or infectious conditions that might interfere with the erythropoietin response
6. Received red blood cell transfusions within 12 weeks before screening or during the screening/ baseline period
7. C-reactive protein >30 mg/L
8. The likelihood of early withdrawal or life expectancy of <12 months
9. Poor compliance with dialysis treatment, evidenced by more than two missed treatment monthly over the previous 3 months
10. Refuse to be involved in the study

STATISTICAL ANALYSIS

Data were described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. To determine whether the data were normally distributed, a Kolmogorov-Smirnov test was used. Comparison of quantitative variables between the study groups was done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test was performed and exact test was used when the

expected frequency is less than 5. Logistic regression analysis was used for analysis of independent factor with the outcome of the patients. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using (Statistical Package for the Social Science)SPSS 21version (SPSS Inc., Chicago, IL, USA)statistical program for Microsoft Windows.

OBSERVATIONS AND RESULTS

This was an open-label, single centre, randomized, parallel-group study, conducted in patients undergoing maintenance hemodialysis at DMCH Dialysis centre from May 2020– May 2021. 100 patients on maintenance dialysis were included in the study and were randomized into two groups, one receiving conventional Erythropoietin alfa/beta intravenous (IV) three times a week and the other receiving CERA once in two weeks. The study population was followed up for 24 weeks

BASELINE CHARACTERISTICS OF PATIENTS

TABLE 1.0 AGE AND BMI DISTRIBUTION OF PATIENTS

	EPO		CERA		t	p-value
	Mean	SD	Mean	SD		
AGE	58.48	13.42	55.36	8.54	1.387	0.169
WEIGHT	62.74	6.99	65.24	8.11	-1.651	0.102
BMI (kg/m2)	21.18	1.49	21.83	2.23	-1.727	0.087

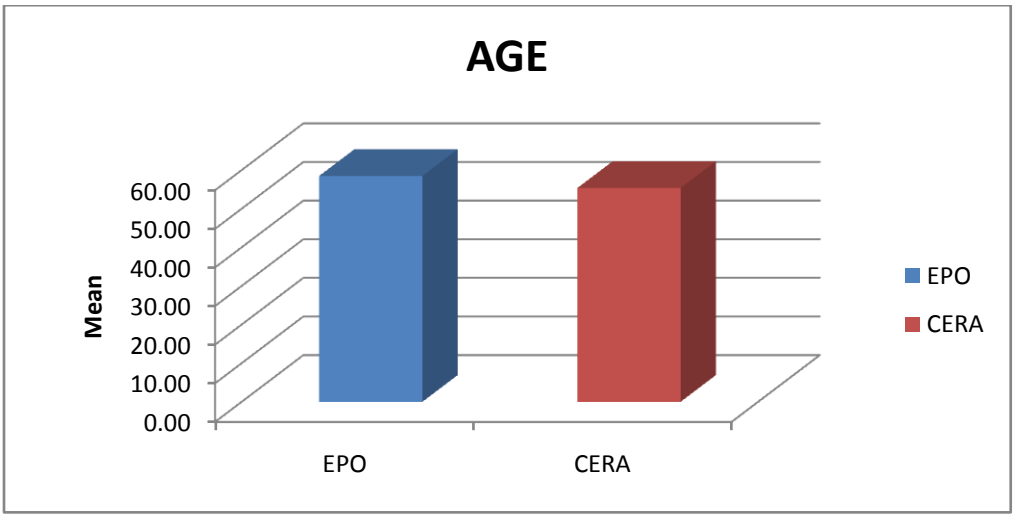


Fig 1.0 Age distribution of patients

In baseline characteristics, mean age was 58.48±13.42 years in EPO group and 55.36±8.54 in CERA group.

TABLE 1.1 AGE GROUP DISTRIBUTION OF PATIENTS

		EPO		CERA		Total	Chi-square value	p-value
		Number of pts.	%	Number of pts.	%			
AGE GROUP	20-40	6	12%	2	4%	8	4.134	0.127
	41-60	26	52%	35	70%	61		
	> 60	18	36%	13	26%	31		
Total		50	100%	50	100%	100		

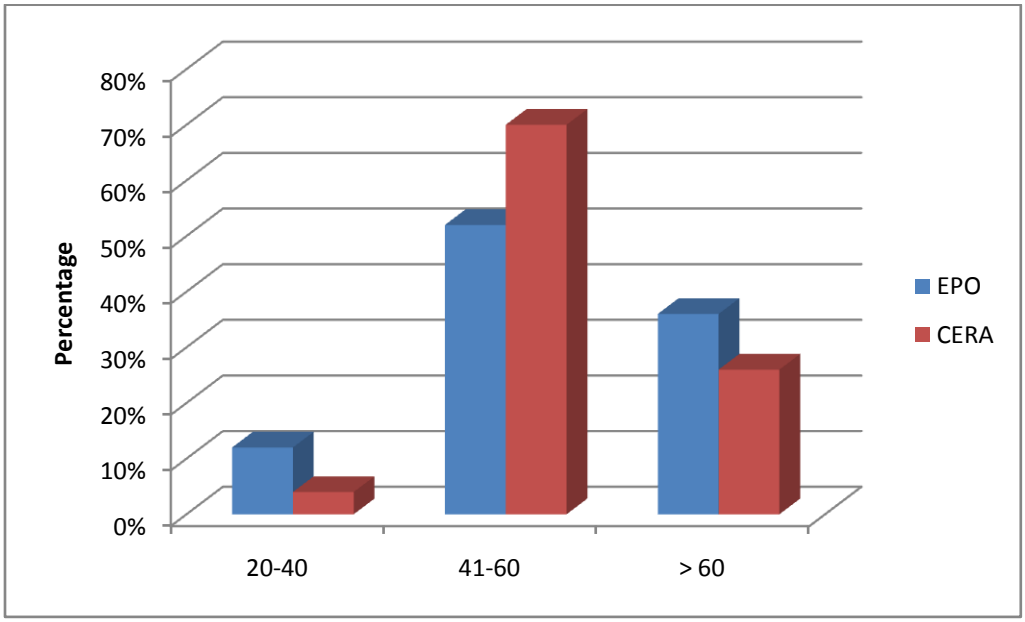


Fig 1.1 Group wise age distribution of patients

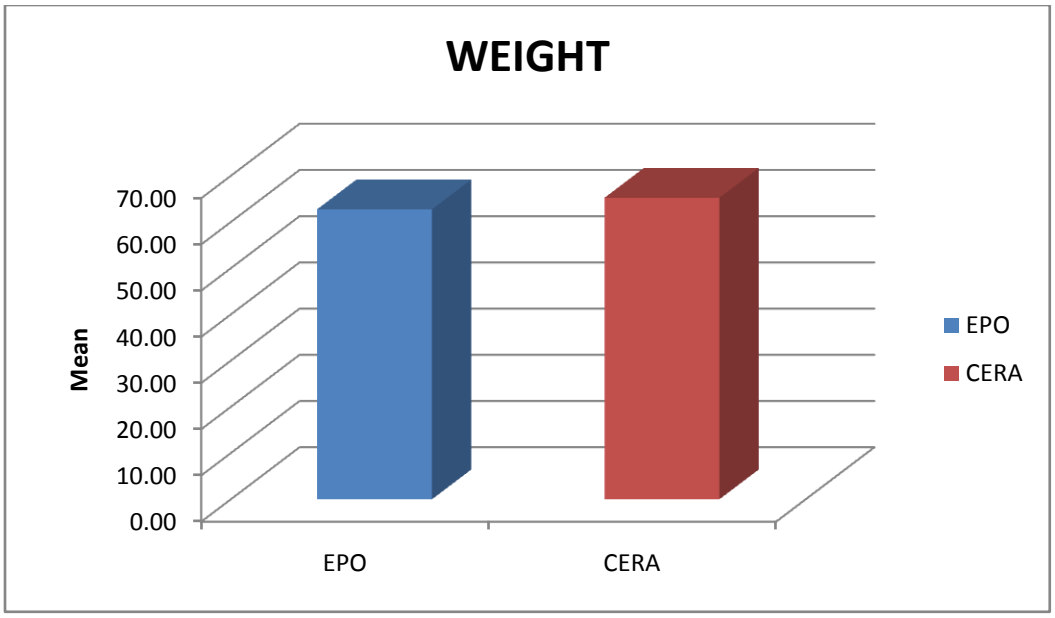


Fig 1.2 Weight distribution of patients

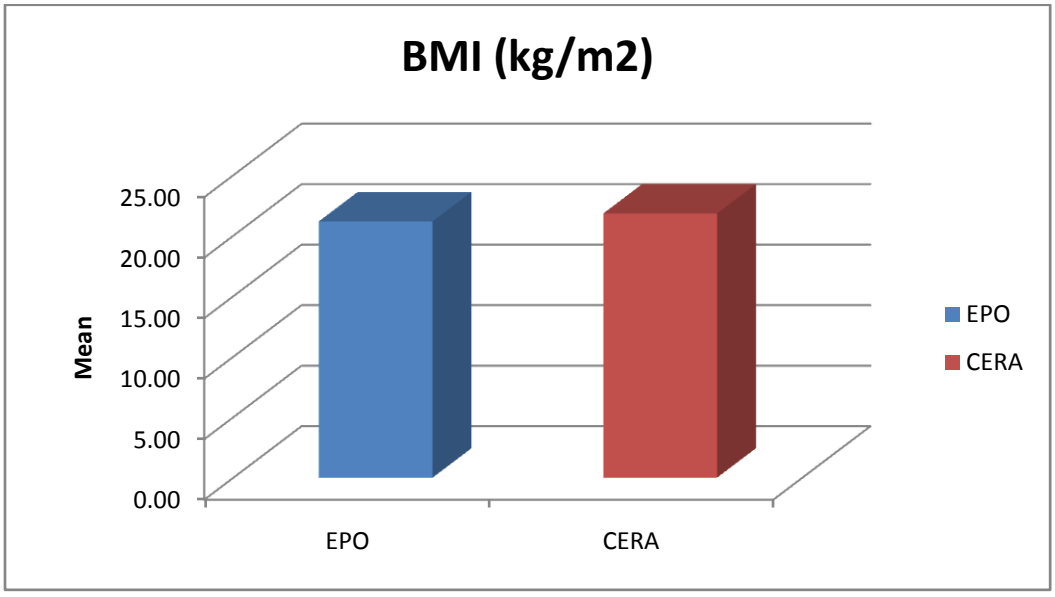


Fig 1.3 BMI distribution of patients

Mean BMI (Kg/m^2) was 21.18±1.49 in EPO group and 21.83±2.23 in CERA group. Both the differences in age and BMI were statistically insignificant.

TABLE 1.2 GROUP WISE BMI DISTRIBUTION OF PATIENTS

		EPO		CERA			Chi-square value	p-value
		Number of patients	%	Number of patients	%	Total		
BMI GROUP	< 23	41	82%	35	70%	76	1.974	0.241
	23-29	9	18%	15	30%	24		
Total		50	100%	50	100%	100		

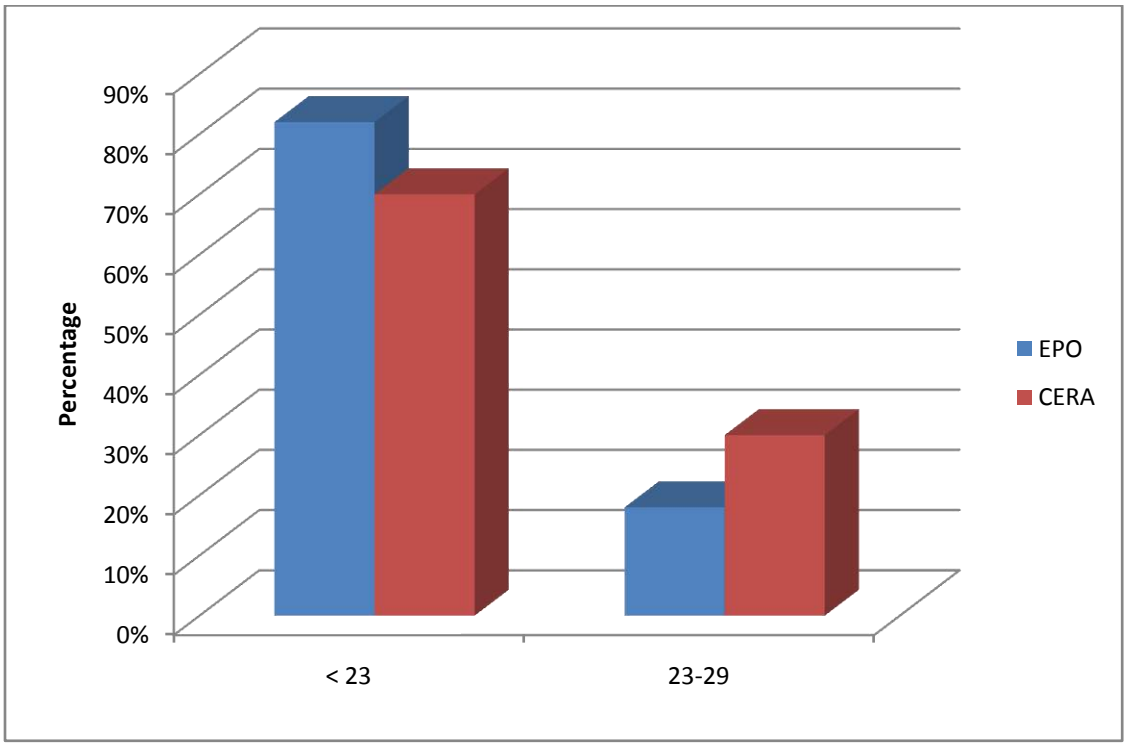


Fig 1.4 Group wise BMI distribution of patients

TABLE 2.0 SEX DESTRIBUTION OF PATIENTS

		EPO group		CERA group		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	%age			
SEX	F	14	28%	17	34%	31	0.421	0.517
	M	36	72%	33	66%	69		

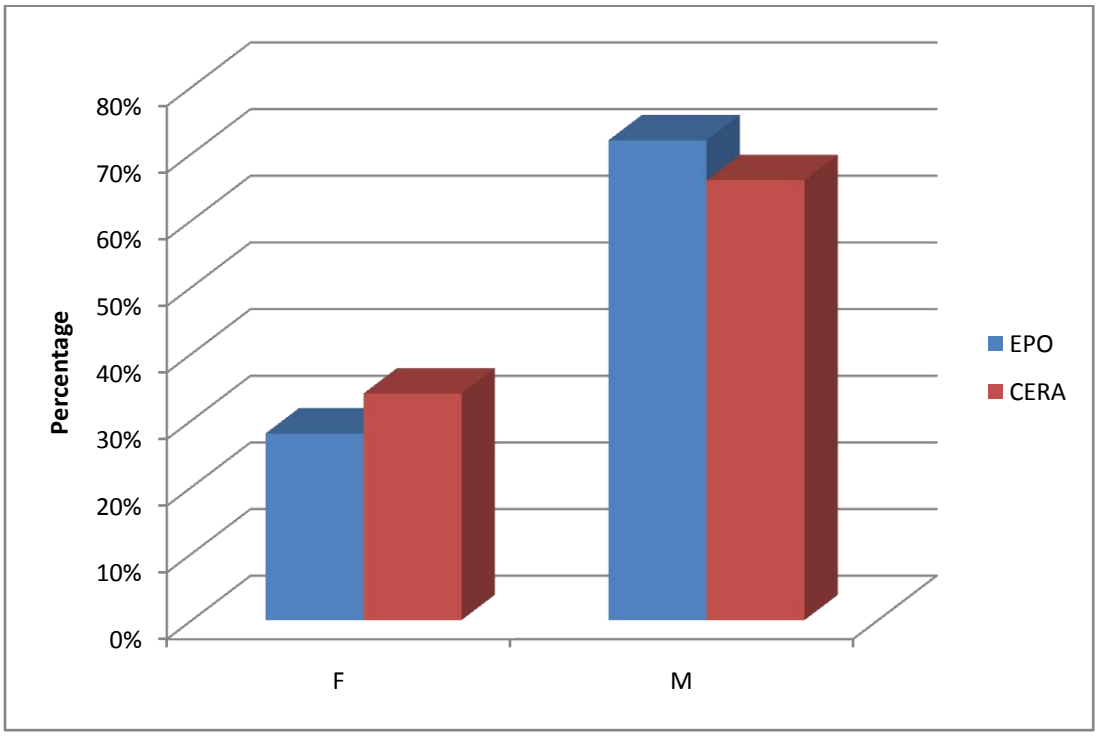


Fig 2.0 Sex distribution of patients

Male preponderance was seen in both the groups with 36 (72%) in EPO group and 33 (66%) in CERA group. The difference was statistically insignificant**.**

TABLE 3.0 BASIC DISEASES IN STUDY POPULATION

		EPO		CERA		Total
		No. of cases	%age	No. of cases	%age	
BASIC DISEASE	ANTI GBM	1	2%	0	0%	1
	CGN	11	22%	7	14%	18
	AMYLOIDOSIS	1	2%	0	0%	1
	ANCA VASCULITIS	0	0%	2	4%	2
	CIN	1	2%	3	6%	3
	NEPHROLITHIASIS	2	4%	6	12%	8
	BPH-OBSTRUCTIVE NEPHROPATHY	1	2%	1	2%	2
	MULTIPLE MYELOMA CAST NEPHROPATHY	2	4%	0	0%	2
	VUR	0	0%	1	2%	1
	DIABETIC KIDNEY DISEASE	21	42%	18	36%	39
	HYPERTENSIVE NEPHROSCLEROSIS	10	20%	10	20%	20
	OTHERS	0	0%	2	4%	2

Among other Basic disease, Diabetic kidney disease was the most common with 21(42%) patients in EPO group and 18(36%) patients in CERA group, followed by Hypertensive nephrosclerosis with 10 (20%) patients in EPO and 10 (20%) patients in CERA group.11 patients (22%) in EPO group and 7 patients (14%) in CERA group had CGN as the cause for CKD, which was the third most common cause in our study population. Among other causes, 2 patients in CERA group had ANCA vasculitis, 1 patient had Amyloidosis in EPO group. 1 patient in EPO group had Anti-GBM disease. 1 patient in EPO group and 3 patients in CERA group had CIN.

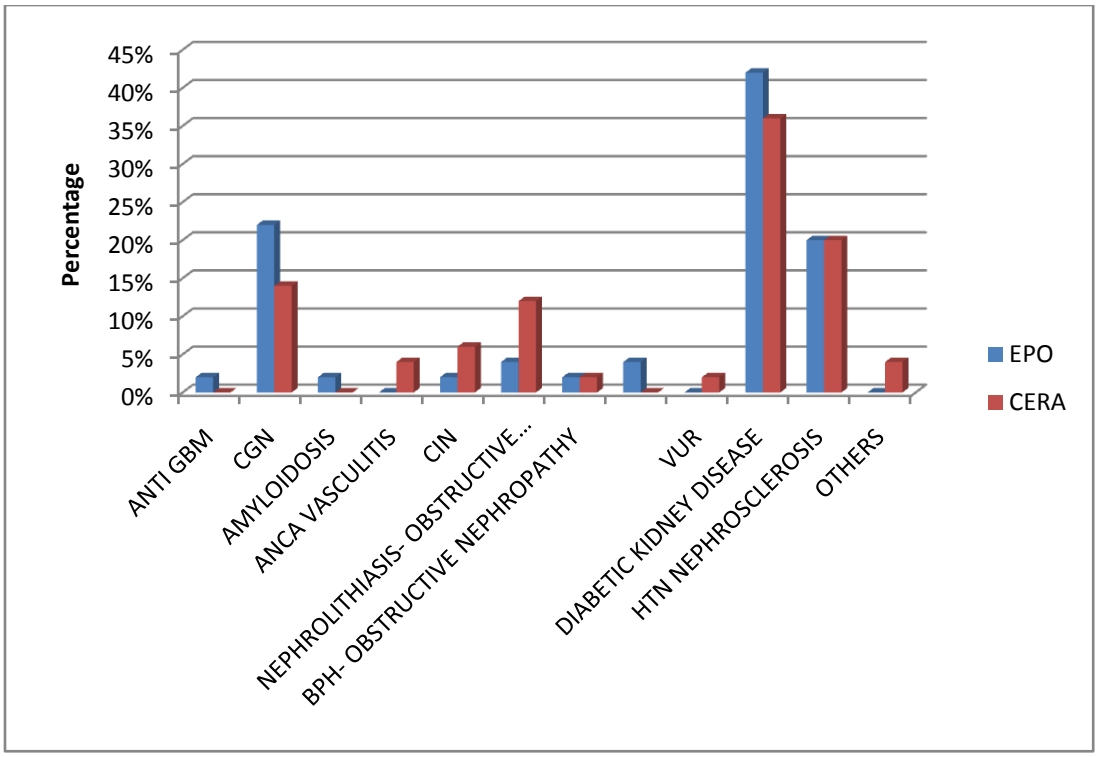


Fig 3.0 Basic disease distribution in EPO and CERA groups.

TABLE 3.1 OTHER CO-MORBIDITIES IN STUDY POPULATION

		EPO		CERA		Total
		No. of cases	%age	No. of cases	%age	
OTHER COMORBIDITIES	CLD	0	0%	2	4%	2
	CAD	9	18%	7	14%	14
	OLD CVA	1	2%	1	2%	2

2 patients (4%) in CERA group had Chronic Liver Disease (CLD). 9 patients (18%) in EPO group and 7 patients (14%) in CERA group had CAD. 1 patient (2%) in each EPO and CERA group had history of CVA**.**

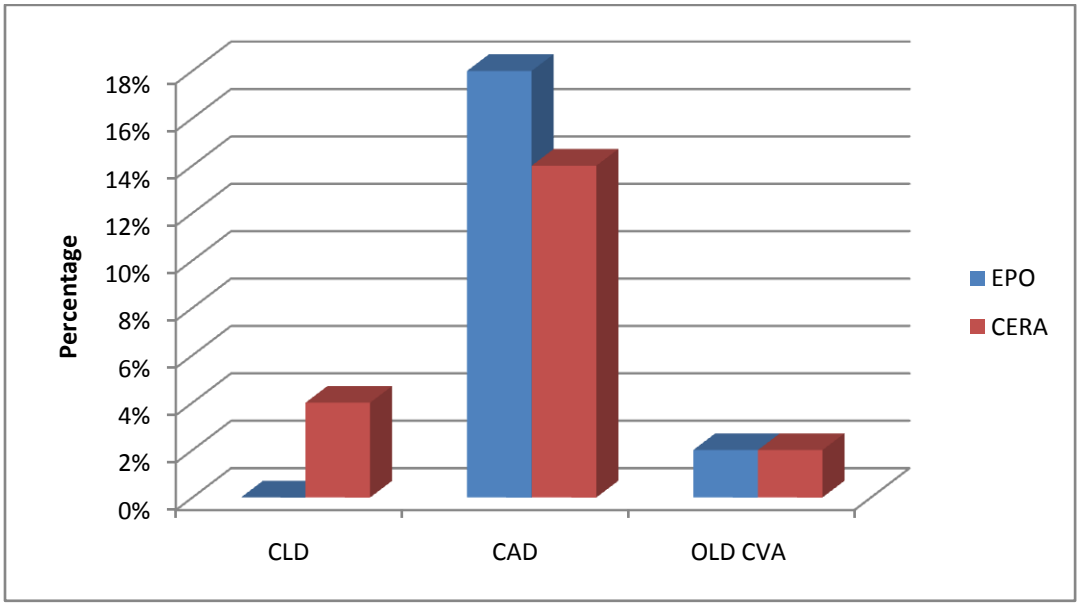


Fig 3.1 Co-morbidity distribution in study population.

TABLE 3.2 HYPERTENSIVE PATIENT DISTRIBUTION

		EPO		CERA		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	%age			
HTN	N	9	18%	4	8%	13	2.21	0.234
	Y	41	82%	46	92%	87		

41 (82%) patients in EPO group and 46 (92%) Patients in CERA group were Hypertensive (p value 0.234).

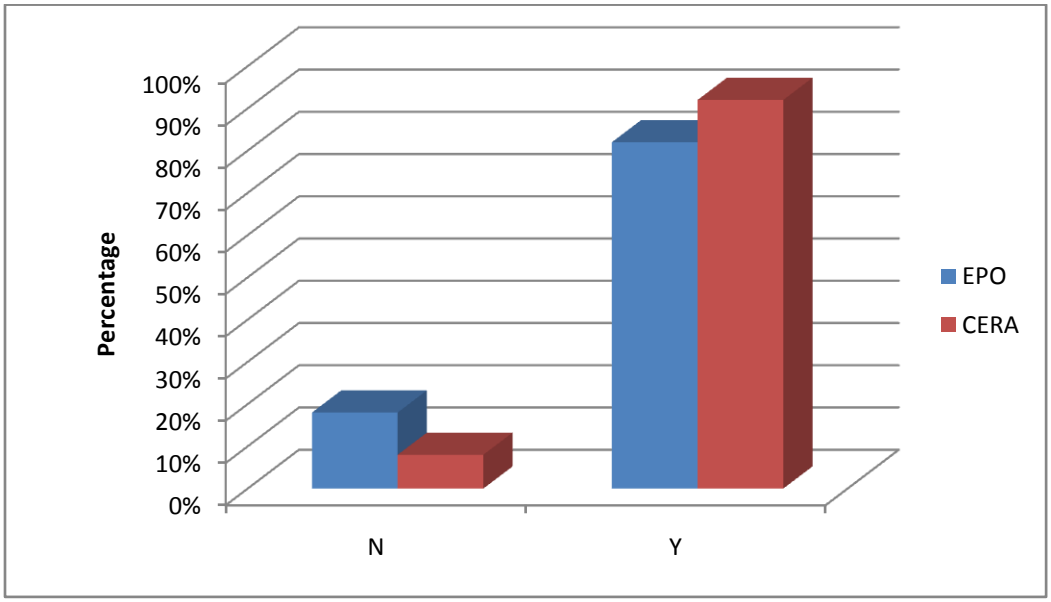


Fig 3.2 Hypertensive patient distribution

TABLE 3.3 DIABETIC PATIENT DISTRIBUTION

		EPO		CERA		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	%age			
DM	N	28	56%	23	46%	51	3.533	0.171
	Y	22	44%	27	54%	49		

22(44%) patients in EPO group and 27(54%) patients in CERA group were Diabetic (p value 0.171)

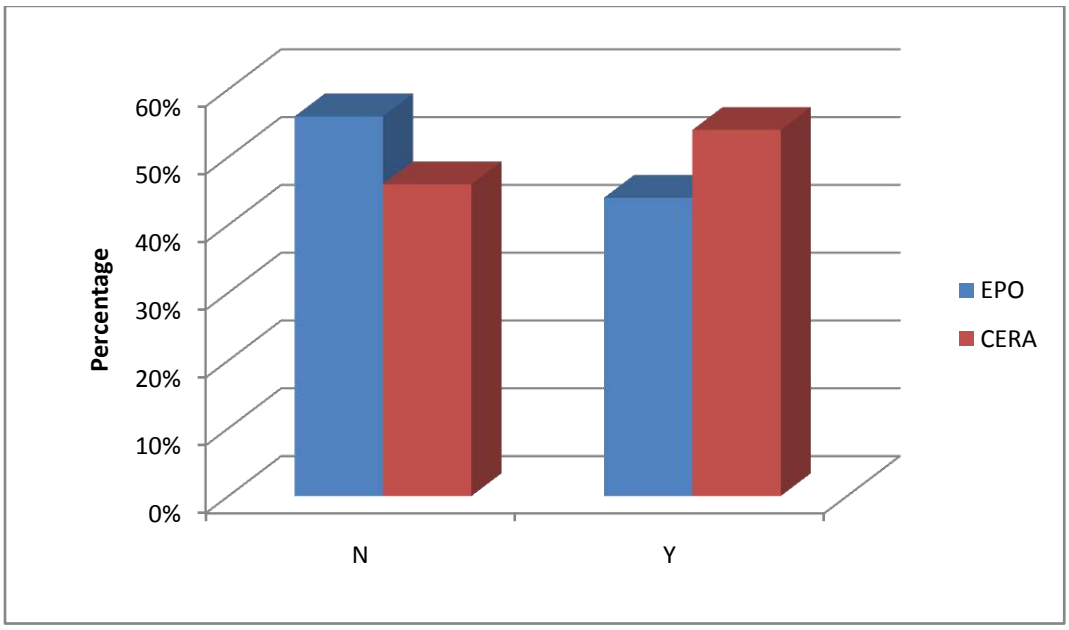


Fig 3.3 Diabetic patient distribution

TABLE 4.0 DIALYSIS VINTAGE (MEAN)

	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
dialysis vintage (weeks)	23.66	11.74	24.06	10.70	-0.178	0.859

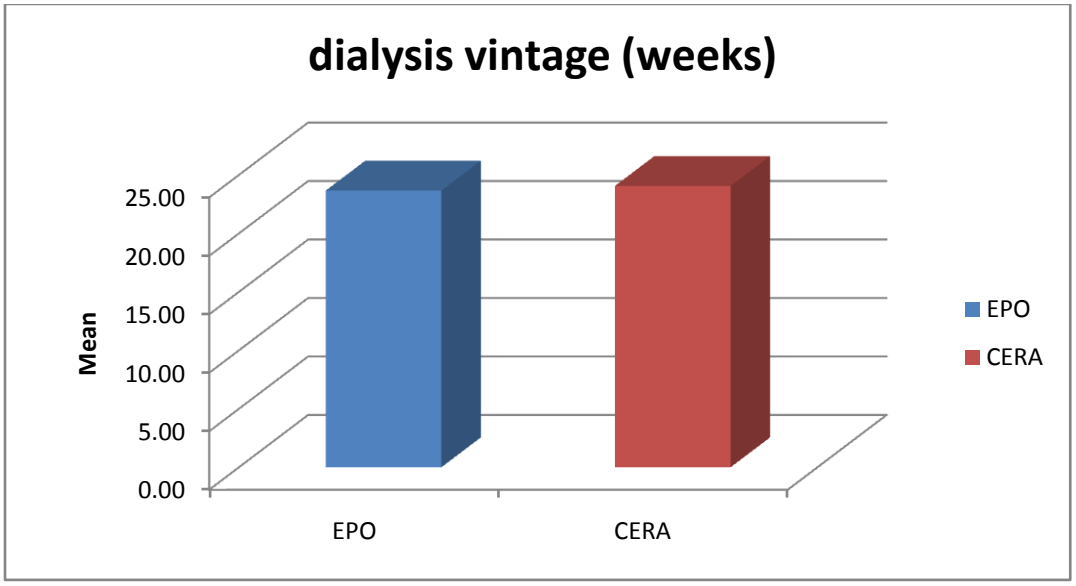


Fig 4.0 Dialysis vintage (mean)

Mean dialysis vintage was 23.66 ± 11.74 weeks in EPO group and 24.06 ± 10.70 weeks in CERA group. Difference between both groups was insignificant (p value >0.05).

TABLE 4.1 GROUP WISE DISTRIBUTION OF DILAYSIS VINTAGE

		EPO		CERA		Total	Chi-square value	p-value
		Number of patients	%	Number of patients	%			
Dialysis vintage (weeks) GROUP	< 24	26	52%	22	44%	48	1.177	0.555
	24-48	22	44%	27	54%	49		
	> 48	2	4%	1	2%	3		
Total		50	100%	50	100%	100		

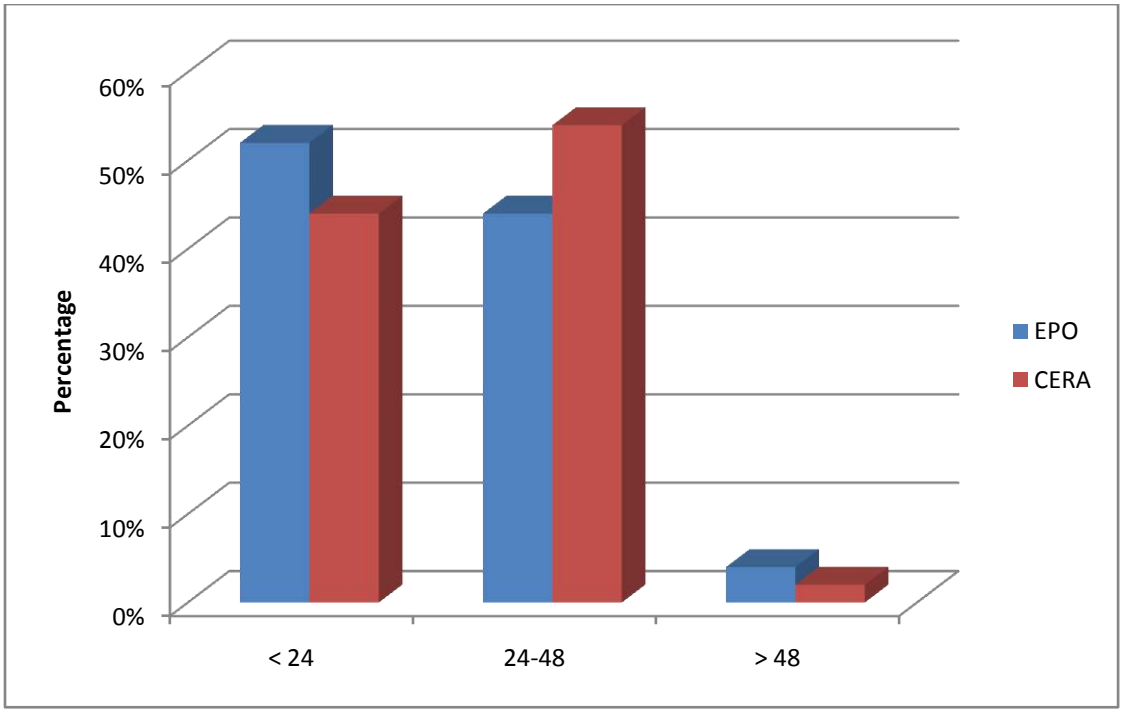


Fig 4.1 Group wise distribution of Dialysis vintage

TABLE 4.2 DIALYSIS VINTAGE (MEDIAN)

	EPO		CERA		Z	p-value
	Median	IQR	Median	IQR		
Dialysis vintage (weeks)	22	16-28	24	15.75-32	-0.486	0.627

Median dialysis vintage was 22 weeks in EPO group and 24 weeks in CERA group (p value was insignificant).

TABLE 5.0 BASELINE HEMOGLOBIN (MEAN)

	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
Hb_0	8.51	0.32	8.46	0.29	0.960	0.339

Mean baseline hemoglobin (Hb) was 8.51±0.32 g/dl in EPO group and 8.46±0.29 g/dl in CERA group respectively. This difference was statistically insignificant (p value >0.05)

TABLE 5.1 BASELINE HEMOGLOBIN (MEDIAN)

	EPO		CERA		Z	p-value
	Median	IQR	Median	IQR		
Hb_0	8.6	8.3-8.8	8.45	8.2-8.6	-2.056	0.060

Median baseline Hb was 8.50 g/dl in EPO group and 8.45 g/dl in CERA group, which was statistically insignificant.

TABLE 6.0 BASELINE TRANSFERRIN SATURATION (MEAN)

	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
tsat(%)_0	37.40	8.71	38.35	9.15	-0.621	0.535

Baseline mean t sat was 37.40 ± 8.71 in EPO group and 38.35±9.15 in CERA group

TABLE 6.1 BASELINE TRANSFERRIN SATURATION (MEDIAN)

	EPO		CERA		Z	p-value
	Median	IQR	Median	IQR		
tsat(%)_0	35.2	32.375-40.175	37	31.9-40.55	-0.621	0.535

Baseline median t sat was 35.2% in EPO group and 37% in CERA group. The difference was statistically insignificant (p value >0.05).

TABLE 6.2 BASELINE FERRITIN (MEAN)

	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
ferritin_0	679.24	282.67	633.36	122.87	-0.887	0.375

Baseline mean ferritin was 679.24 ± 282.6 ng/ml in EPO group and 633.36±122.8 ng/ml in CERA group. The difference was statistically insignificant (p value >0.05).

TABLE 6.3 BASELINE FERRITIN (MEDIAN)

	EPO		CERA		Z	p-value
	Median	IQR	Median	IQR		
ferritin_0	630	605-679.25	611.5	546-700.25	-0.887	0.375

Baseline median ferritin was 630 ng/ml in EPO group and 611 ng/ml in CERA group. The difference was statistically insignificant (p value >0.05).

TABLE 7.0 BASELINE B12 AND FOLATE (MEAN)

	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
B12	1283.74	480.15	1690.44	449.81	-3.790	0.000
	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
FOLATE	8.05	1.92	8.44	2.43	-0.211	0.833
	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
CRP	3.08	2.00	2.97	1.83	-0.079	0.937

Mean baseline B12 was 1283.7± 489.15 in EPO group and 1690.44± 449.81 in CERA group. The difference was statistically significant although B12 values were sufficient in both the groups.

Mean baseline Folate was 8.05± 1.92 in EPO group and 8.44 ±2.43 in CERA group. The difference was statistically insignificant (p value >0.05)

Mean baseline CRP was 3.08± 1.92 in EPO group and 2.97 ±1.83 in CERA group. The difference was statistically insignificant (p value >0.05).

TABLE 7.1 BASELINE B12 AND FOLATE (MEDIAN)

	EPO		CERA		Z	p-value
	Median	IQR	Median	IQR		
B12	1200	982-1850	2000	1210-2000	-3.790	0.000
	EPO		CERA		Z	p-value
	Median	IQR	Median	IQR		
FOLATE	8.2	6.8-9.1	8.05	6.8-8.9	-0.211	0.833
	EPO		CERA		Z	p-value
	Median	IQR	Median	IQR		
CRP	2.4	1.2-5	2.3	1.5-4.5	-0.079	0.937

Median baseline B12 was 1200.0 in EPO group and 2000in CERA group . The difference was statistically significant although B12 values were sufficient in both the groups.

Median baseline Folate was 8.2 in EPO group and 8.05 in CERA group . the difference was statistically insignificant (p value >0.05)

Median baseline CRP was 2.4 in EPO group and 2.3 in CERA group . The difference was statistically insignificant (p value >0.05)

TABLE 7.2 DIALYSIS ADEQUACY

	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
kt/v	1.45	0.20	1.45	0.16	-0.003	0.997

Mean kt/v was 1.45 in EPO group and 1.44 in CERA group. The difference was statistically insignificant. (p value >0.05)

TABLE 8.0 EFFICACY OUTCOME- HEMOGLOBIN (Hb) RESPONSE RATES

		EPO		CERA		Total	Chi-square value	p-value
		EPO	EPO	CERA	CERA			
hb response (y/n)	N	5	10%	9	18%	14	1.329	0.249
	Y	45	90%	41	82%	86		

45 patients (90%) in EPO group and 41(82%) patients in CERA group had Hb response based on the defined criteria. The difference was statistically insignificant (p value >0.05).

TABLE 8.1 EFFICACY OUTCOME – TIME TO HEMOGLOBIN (Hb) RESPONSE (MEAN)

	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
time to hb response (weeks)	8.09	2.86	10.54	2.93	-4.097	0.000

Mean time to Hb response was 8.09± 2.86 weeks in EPO group and 10.54± 2.93 weeks in CERA group. The difference was statistically significant (p value <0.05)

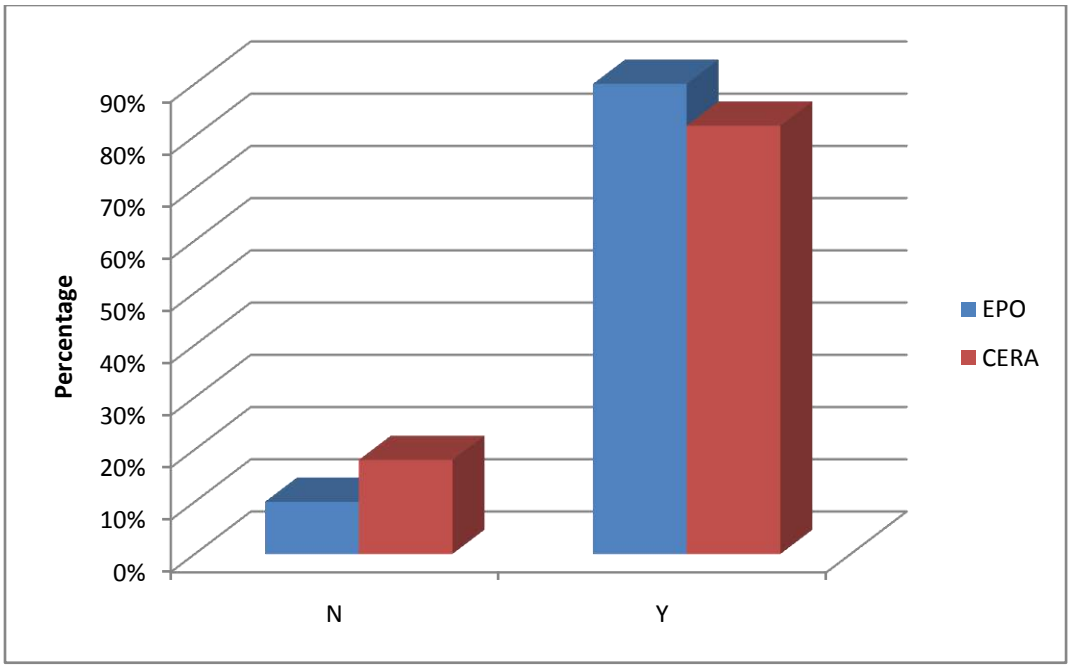


Fig 5.0 Hb Response rates

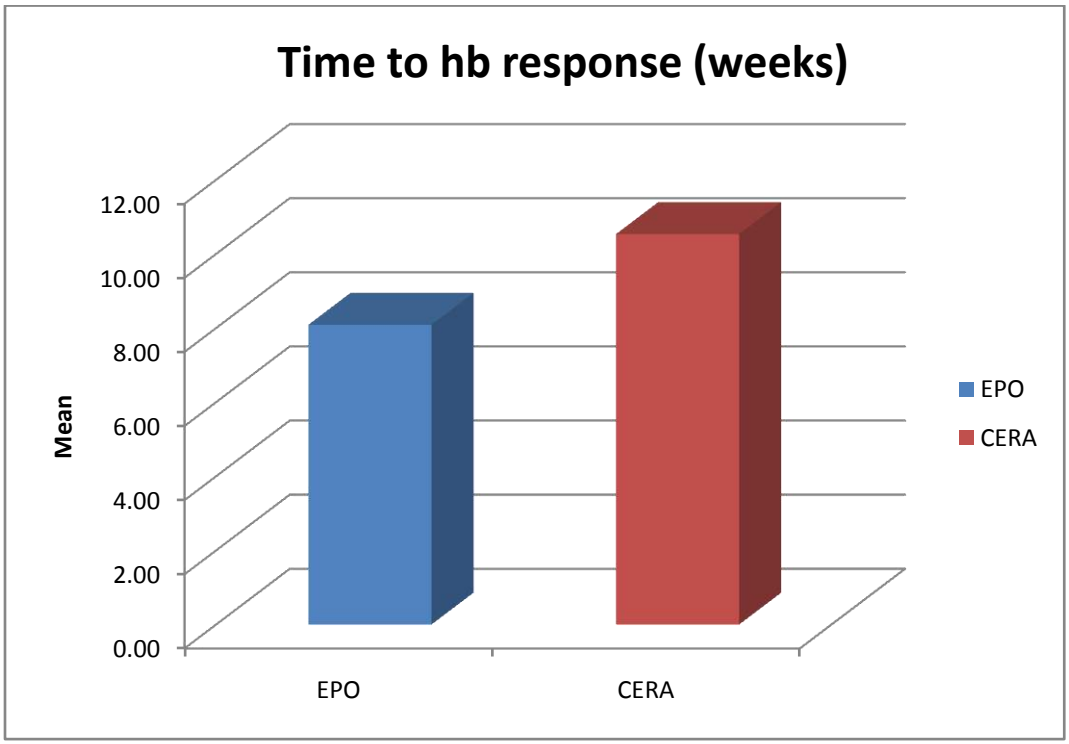


Fig 5.1 Mean time to Hb response (weeks)

TABLE 8.2 EFFICACY OUTCOME – TIME TO HEMOGLOBIN (Hb) RESPONSE (MEDIAN)

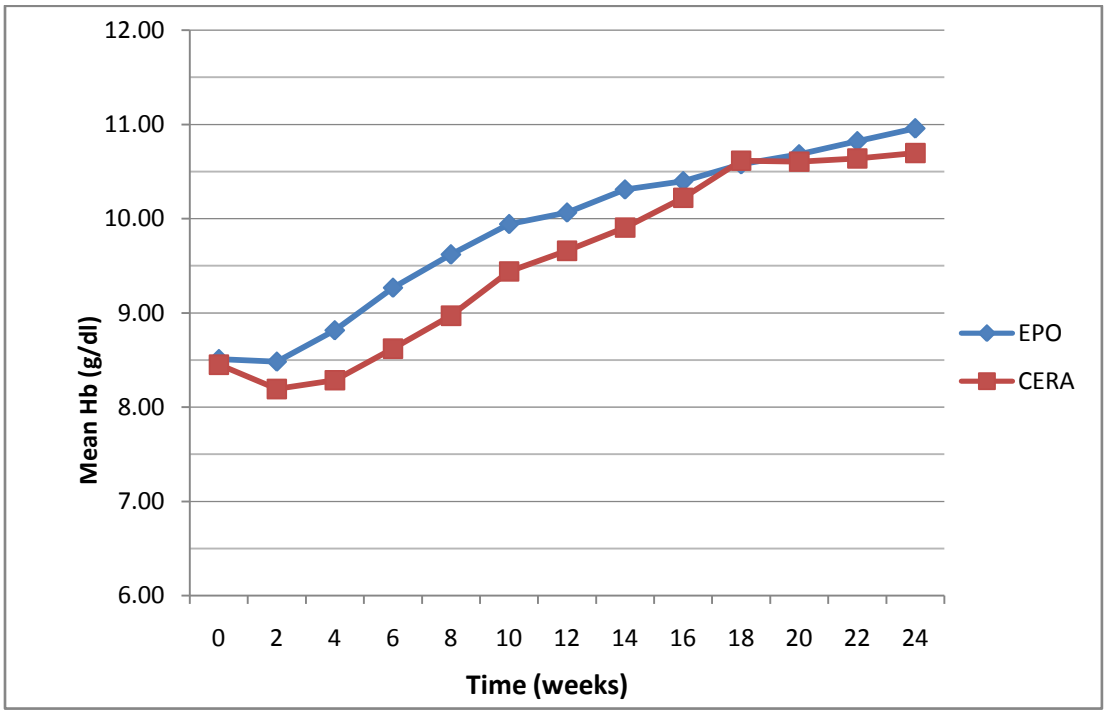
	EPO		CERA		Z	p-value
	Median	IQR	Median	IQR		
time to hb response (weeks)	8	6-10	10	8-12	-4.097	0.000

Median time to Hb response was 8 weeks in EPO group and 10 weeks in CERA group. The difference was statistically significant (p value<0.05).

TABLE 8.3 CHANGE OF MEAN HEMOGLOBIN WITH TIME

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
Hb_0	EPO	50	8.51	0.32	0.04	8.42	8.60	8.00	9.00
	CERA	50	8.46	0.29	0.04	8.37	8.54	8.10	9.40
	Total	100	8.49	0.30	0.03	8.43	8.54	8.00	9.40
Hb_2	EPO	50	8.48	0.46	0.07	8.35	8.61	7.60	9.30
	CERA	50	8.19	0.46	0.07	8.06	8.32	7.00	9.30
	Total	100	8.34	0.48	0.05	8.24	8.43	7.00	9.30
Hb_4	EPO	50	8.81	0.60	0.08	8.64	8.98	7.10	9.90
	CERA	50	8.29	0.53	0.07	8.14	8.44	7.10	9.50
	Total	100	8.55	0.62	0.06	8.43	8.67	7.10	9.90
Hb_6	EPO	50	9.27	0.63	0.09	9.09	9.44	7.50	10.50
	CERA	49	8.62	0.64	0.09	8.44	8.81	7.20	9.90
	Total	99	8.95	0.71	0.07	8.80	9.09	7.20	10.50
Hb_8	EPO	50	9.62	0.79	0.11	9.39	9.84	7.30	11.50
	CERA	49	8.97	0.73	0.10	8.76	9.18	7.00	10.50
	Total	99	9.30	0.82	0.08	9.13	9.46	7.00	11.50
Hb_10	EPO	50	9.94	0.87	0.12	9.69	10.19	7.80	12.30
	CERA	48	9.44	0.73	0.11	9.23	9.65	7.80	10.80
	Total	98	9.70	0.84	0.08	9.53	9.86	7.80	12.30
Hb_12	EPO	50	10.06	0.89	0.13	9.81	10.32	8.00	11.90
	CERA	48	9.66	0.84	0.12	9.41	9.90	8.00	11.30
	Total	98	9.87	0.88	0.09	9.69	10.04	8.00	11.90

Hb_14	EPO	49	10.31	0.89	0.13	10.05	10.56	8.50	12.30
	CERA	48	9.90	1.02	0.15	9.61	10.20	7.80	11.70
	Total	97	10.11	0.97	0.10	9.91	10.30	7.80	12.30
Hb_16	EPO	49	10.40	0.84	0.12	10.16	10.64	8.30	11.80
	CERA	48	10.22	1.15	0.17	9.89	10.55	7.90	12.30
	Total	97	10.31	1.00	0.10	10.11	10.51	7.90	12.30
Hb_18	EPO	49	10.58	0.91	0.13	10.31	10.84	8.60	12.20
	CERA	47	10.61	1.20	0.17	10.26	10.97	7.60	12.60
	Total	96	10.59	1.06	0.11	10.38	10.81	7.60	12.60
Hb_20	EPO	48	10.68	0.93	0.13	10.41	10.95	8.70	12.50
	CERA	46	10.60	1.15	0.17	10.26	10.94	7.80	12.30
	Total	94	10.64	1.03	0.11	10.43	10.86	7.80	12.50
Hb_22	EPO	47	10.82	0.77	0.11	10.60	11.05	9.00	12.40
	CERA	46	10.64	1.19	0.18	10.29	10.99	7.90	12.60
	Total	93	10.73	1.00	0.10	10.53	10.94	7.90	12.60
Hb_24	EPO	47	10.96	0.85	0.12	10.71	11.21	8.90	12.50
	CERA	46	10.70	1.11	0.16	10.37	11.02	8.00	12.60
	Total	93	10.83	0.99	0.10	10.62	11.03	8.00	12.60
time to hb response (week)	EPO	45	8.09	2.86	0.43	7.23	8.95	4.00	16.00
	CERA	41	10.54	2.93	0.46	9.61	11.46	6.00	20.00
	Total	86	9.26	3.13	0.34	8.58	9.93	4.00	20.00



GRAPHS 1.0 MEAN Hb CHANGES FROM BASELINE OVER TIME

TABLE 8.4 EFFICACY OUTCOMES- Hb RESPONSE IN DIABETIC VS NON-DIABETIC PATIENTS TO INTERVENTION.

		DM		Total	Chi-square value	p-value
		N	Y			
hb response (y/n)	N	2	9	11	9.093	0.011
	NA	0	3	3		
	Y	49	37	86		
Total		51	49	100		

Out of total 49 diabetic patients , 37(75%) patients showed response to Erythropoetin therapy (EPO or CERA) as compared to 49 (96%) out of total 51 non-diabetic patients. This difference in response was statistically significant (p value <0.05).

TABLE 8.5 EFFICACY OUTCOME – GROUP WISE HEMOGLOBIN RESPONSE IN DIABETIC VS NON-DIABETIC PATIENTS

Group			DM		Total	Chi-square value	p-value
			N	Y			
EPO	hb response (y/n)	N	2	3	5	0.577	0.643
		Y	26	19	45		
	Total		28	22	50		
CERA	hb response (y/n)	N	0	6	6	9.35	0.009
		NA	0	3	3		
		Y	23	18	41		
	Total		23	27	50		

19 out of 22 diabetic patients in EPO group showed Hb response to therapy. No significant difference in response to EPO was found between diabetic and non diabetic patients (p value >0.05)

18 out of 27 patients in CERA group showed Hb response to therapy. Low response rates were found to CERA in diabetic patients, which was statistically significant (p value <0.05)

TABLE 8.6 TIME TO Hb RESPONSE IN DIABETIC PATIENTS

DM	N		Y		Z	p-value
	Mean	SD	Mean	SD		
time to hb response (week)	9.27	2.760	9.24	3.60	0.032	0.974

Mean time to Hb response to Erythropoetin therapy (EPO/CERA) was 9.24± 2.76 weeks in Diabetics and 9.27±3.60 weeks in non-Diabetic patients. The difference was statistically insignificant (p value >0.05)

TABLE 8.7 EFFICACY OUTCOME- NEED FOR BLOOD TRANSFUSION

		EPO		CERA		Total	Chi-square value	p-value
		No. of patients	EPO%	No. of patients	CERA%			
blood transfusion (y/n)	N	46	92%	45	90%	91	0.122	0.727
	Y	4	8%	5	10%	9		

4 Patients(8%) in EPO group and 5 patients(10%) in CERA group needed Blood Transfusion during correction phase. The difference was statistically insignificant (p value>0.05).

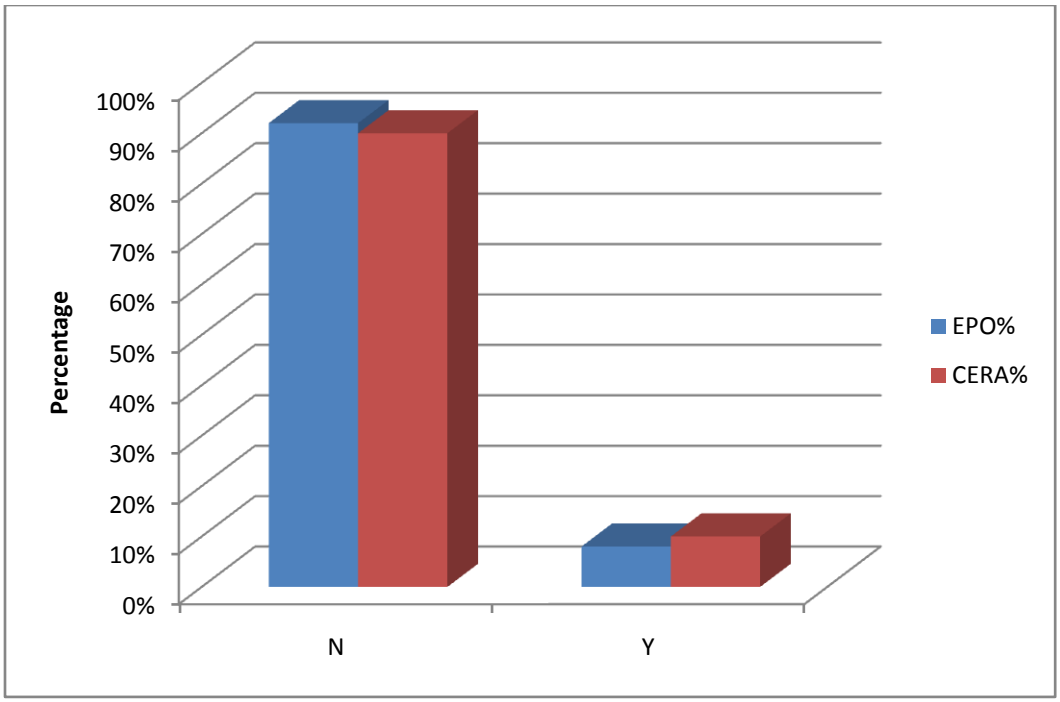
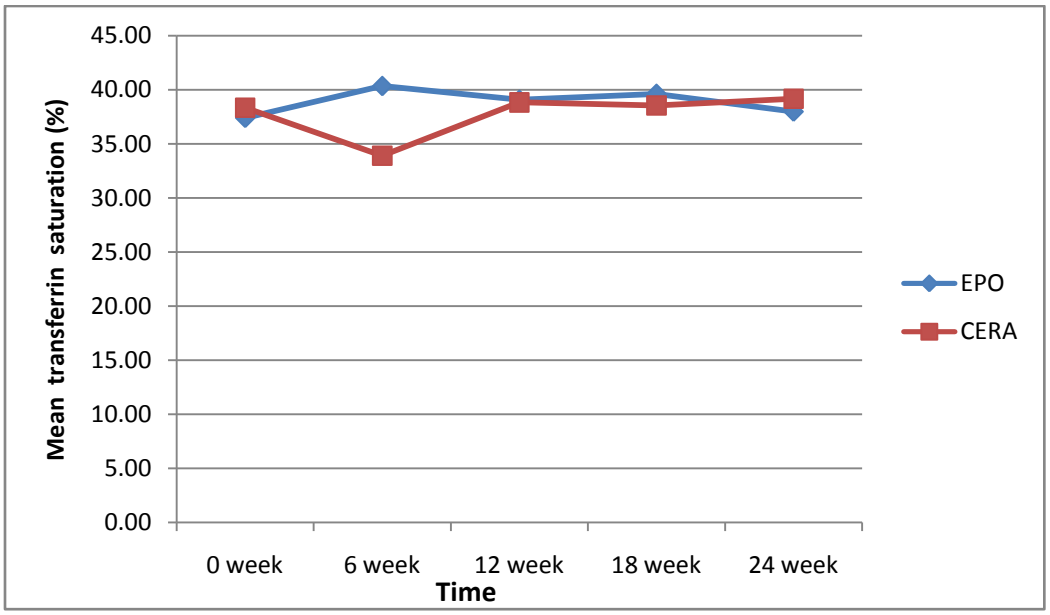


Fig 5.2 NEED FOR BLOOD TRANSFUSION

TABLE 9.0 IRON STUDIES DURING FOLLOWUP- MEAN TRANSFERRIN SATURATION (T SAT %)

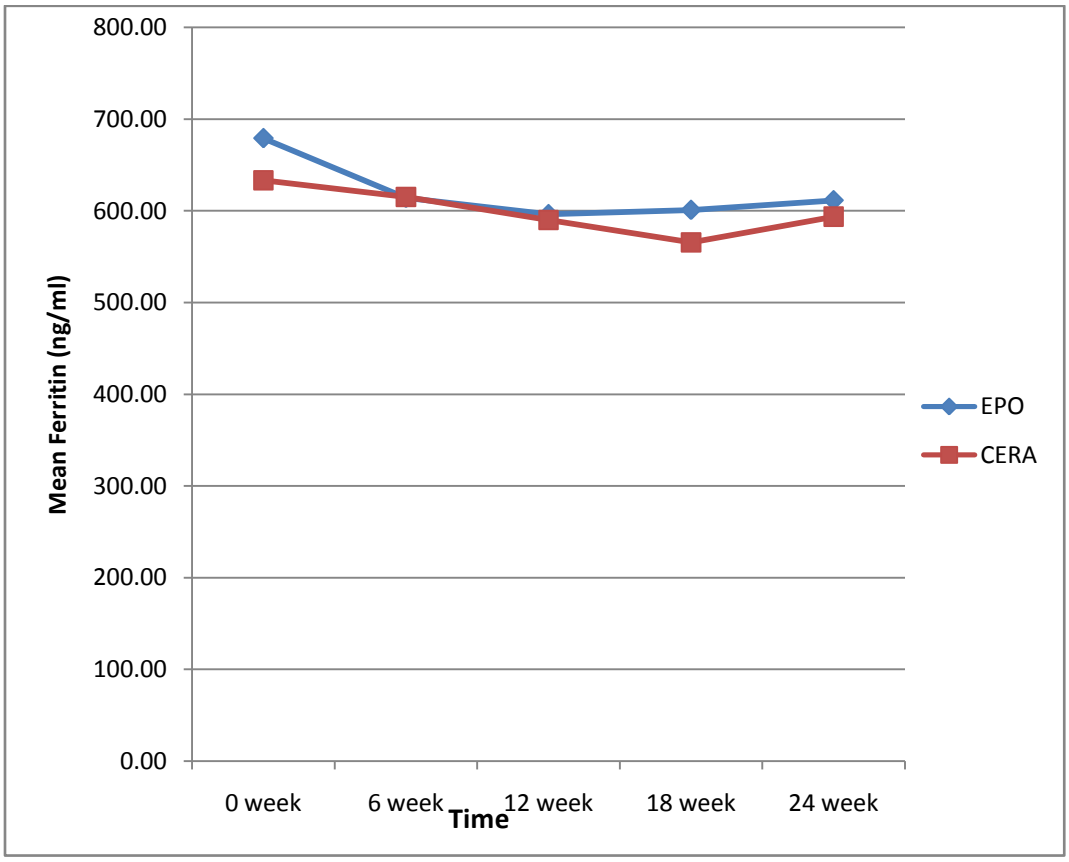
Time (weeks)	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
tsat(%)_0	37.40	8.71	38.35	9.15	-0.621	0.535
tsat(%)_6	40.33	8.82	33.90	9.27	-3.413	0.001
tsat(%)_12	39.06	6.33	38.83	10.37	-1.422	0.155
tsat(%)_18	39.61	8.52	38.54	6.18	-0.308	0.758
tsat(%)_24	37.98	6.45	39.16	6.46	-1.123	0.262



Graph 2.0 Mean transferrin saturation variation over baseline with time

TABLE 9.1 IRON STUDIES DURING FOLLOWUP- MEAN FERRITIN

Time (weeks)	EPO		CERA		Z	p-value
	Mean	SD	Mean	SD		
ferritin_0	679.24	282.67	633.36	122.87	-0.887	0.375
ferritin_6	614.10	101.28	615.18	133.74	-0.291	0.771
ferritin_12	596.38	112.48	590.25	145.71	-0.302	0.763
ferritin_18	601.06	187.26	565.77	90.80	-1.192	0.233
ferritin_24	611.53	148.42	593.80	106.14	-0.227	0.821



Graph 3.0 Mean ferritin variation over baseline with time.

TABLE 10.0 ADVERSE EVENTS

		EPO		CERA		Total	Chi-square value	p-value
		No of patients	EPO%	No of patients	CERA%			
ADVERSE EVENTS	NO	37	74%	33	66%	70	8.474	0.205
	DEATH DUE TO CARDIAC ARREST	0	0%	1	2%	1		
	DEATH DUE TO IC BLEED	0	0%	1	2%	1		
	GI BLEED	1	2%	0	0%	1		
	HIGH BP	8	16%	13	26%	21		
	CAD	2	4%	0	0%	2		
	NEED FOR BT	4	8%	2	4%	6		

Overall the reported AEs during the correction phase were comparable between the two study arms. One patient in each group had death due to cardiac arrest and IC bleed respectively. One patient in EPO group had gi-bleed. 8 patients (16%) in EPO group and 13 patients (26%) in CERA group had uncontrolled hypertension needing adjustment of anti-hypertensive medications, possibly related to EPO/CERA administration; however this difference was not statistically significant. There were 4 patients in EPO group and 2 patients in CERA group with decreased Hb level for which packed RBC were transfused. Anti-EPO antibody was not detected throughout the study

TABLE 10.1 INCIDENCE OF WORSENING HYPERTENSION

		EPO		CERA		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	%age			
ADVERSE EVENT	CONTROLLED BP	42	84%	37	74%	79	1.507	0.220
	WORSENING OF BP	8	16%	13	26%	21		

8 patients (16%) in EPO group and 13 patients (26%) in CERA group had uncontrolled hypertension needing adjustment of anti-hypertensive medications, possibly related to EPO/CERA administration; however this difference was not statistically significant

TABLE 10.2 TOTAL DEATHS

		EPO		CERA		Total	Chi-square value	p-value
		No. of cases	%age	No. of cases	%age			
DEATH	No	47	94%	46	92%	93	0.154	0.695
	YES	3	6%	4	8%	7		
Total		50	100%	50	100%	100		

A total of 3 deaths occurred in EPO group and 4 deaths occurred in CERA group. The difference was statistically not significant (p value >0.05). Deaths were unrelated to Erythropoietin administration.

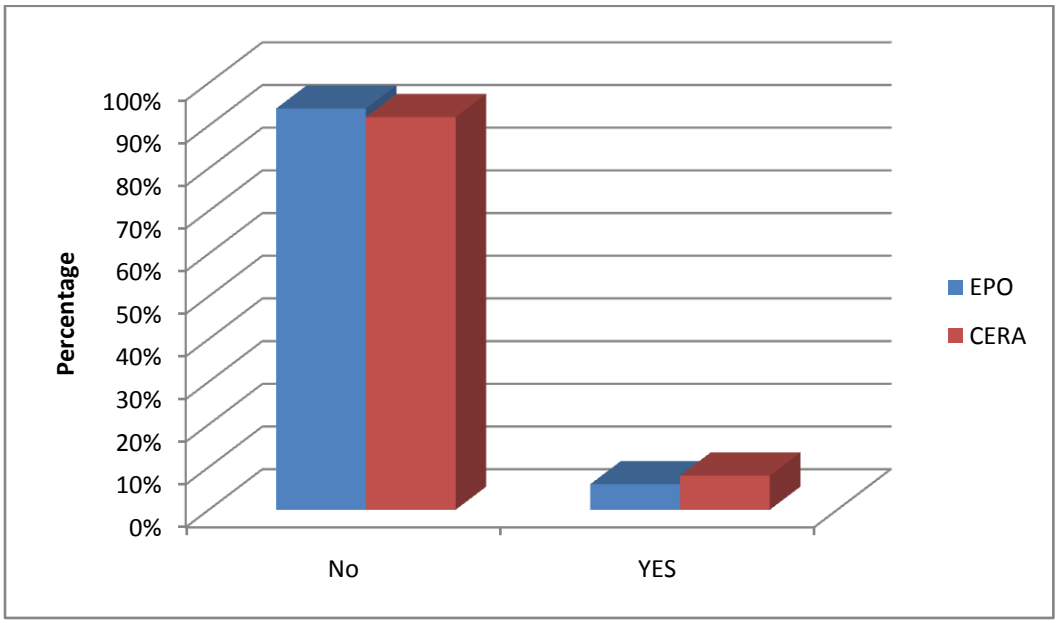


Fig 6.0 Deaths in each group

TABLE 11.0 MULTIVARIATE LOGISTIC REGRESSION ANALYSIS OF TIME TO Hb RESPONSE AND BLOOD TRANSFUSION IN CERA GROUP

CERA	p-value	Odd RATIO	95% C.I.for Odd RATIO	
			Lower	Upper
Blood transfusion	0.524	0.367	0.017	8.045
Time to hb response week	0.001	1.373	1.141	1.652

STUDY DESIGN

ENTRY

INCLUSION CRITERIA

SCREENING PERIOD

2 WEEKS

RANDOMIZATION(1:1)

ERYTHROPOETIN BETA

50 PATIENTS

STARTING DOSE- 40 IU/kg IV, three times per week

CONTINUOUS ERYTHROPOETIN RECEPTOR ACTIVATOR

50 PATIENTS

STARTING DOSE- 0.6 µg/kg of CERA IV once every 2 weeks

24 WEEKS

ERYTHROPOETIN BETA

HB RESPONSE- 90%

MEDIAN TIME TO HB RESPONSE -8 WEEKS

BLOOD TRANSFUSIONS-4

DEATHS-3

CONTINUOUS ERYTHROPOETIN RECEPTOR ACTIVATOR

HB RESPONSE- 82%

MEDIAN TIME TO HB RESPONSE-10 WEEKS

BLOOD TRANSFUSIONS-5

DEATHS-4

DISCUSSION

This study was conducted in patients undergoing maintenance hemodialysis at DMCH Dialysis centre from May 2020– May 2021. It was an open-label, single center, randomized, parallel-group study. 100 patients on maintenance dialysis were included in the study and were randomized into two groups, one receiving conventional erythropoietin alfa/beta intravenous (IV) three times a week and the other receiving CERA once in every two weeks. The study population was followed up for 24 weeks.

This study demonstrated that intravenous CERA once every 2 weeks was as effective as thrice weekly conventional EPO in correcting anemia of long-term dialysis patients during 24 week correction phase. Although, CERA was accompanied by longer time to response than the EPO.

This study had similar design to AMICUS study. [16] Both studies were randomized, open-label, and had a parallel group of IV epoetin alfa or beta three times a week. They were performed to evaluate the efficacy of correction of renal anemia with CERA IV every 2 weeks in patients on maintenance dialysis. In AMICUS study the starting dose was 0.4 μg/kg/2 weeks, and subsequent doses were decided in broader adjustment range (-50%). However, the results were different.

Hb response rates were 82% and 90% for CERA and epoetin beta, respectively in our study. This response rate of CERA group was lower than 93% (95% CI, 87.7-96.9) of CERA group in AMICUS study. Median time to response in both groups was also relatively delayed in our patient population. It was 70 days in CERA group and 56 days in epoetin beta group, which was delayed by approximately 2 to 4 weeks when compared with that in AMICUS study; 57 days (95% CI, 50-64) with CERA and 31 days (95% CI, 27-38) with epoetin.

One of the reasons for these discordances with AMICUS study might be the difference of study population. Ours was a study in Indian population

as compared to AMICUS study which was done in the American population. Also, all patients in our study had received previous EPO therapy. In contrast, only about 30% of the patients had history of previous EPO treatment in AMICUS study. In addition, baseline hemoglobin concentrations were higher in patients of AMICUS study (9.39 ± 0.88 g/dL and 9.40 ± 0.82 g/dL in CERA and epoetin group, respectively) in spite of not receiving EPO in the previous 12 weeks. These facts suggest that overall residual renal function (RRF) in the patients of our study was much lower than that in AMICUS.

In another Asian study conducted in Korea with study design similar to AMICUS study, Hb response rates were 79.5% (95% CI, 63.5-90.7) and 87.8% (95% CI, 73.8-95.9) for CERA and epoetin beta groups respectively.[72] These response rates are similar to what we found in our study. This further supports population variability in erythropoietin response.

Median time to response in the Korean study was 84 days in CERA group and 72 days in epoetin beta group, which was delayed by approximately two weeks when compared to our study. Although both studies were conducted in patients with CKD on dialysis, median dialysis duration of patients in our study was 168 days and 154 days in CERA and epoetin beta group, respectively, which much shorter than the dialysis duration in the Korean study; 621 days in CERA and 590 days in epoetin beta group. Residual renal function (RRF) is known to decline following the initiation of HD. In a retrospective study, Vilar et al. reported the fraction of HD patients who had a residual renal urea clearance ≥ 1 mL/min. At 3 months after initiating HD, this proportion was 85.4%, but it decreased over time to 58.1% at 2 yr and 31.1% at 5 yr. In patients with RRF < 1 mL/min, weekly EPO dose and EPO resistance index were significantly higher from 12 months after the start of HD than in patients with preserved RRF.[74] The presence of RRF in chronic dialysis patients contributes to lower EPO requirement in HD patients. In another study, strong relation between RRF

and improved anemia control in HD patients was reported, suggesting less EPO resistance in patients with high GFR.[75] This could suggest that long-term dialysis patients might need a little higher starting dose of CERA than 0.6 µg/kg/2 weeks to overcome their high EPO resistance. The starting dose of 0.6 µg/kg/2 weeks IV of CERA in this study was based on two phase III studies conducted in CKD patients on dialysis and not on dialysis, AMICUS and ARCTOS, respectively.[16,76] Based on this observation, dose of IV CERA was started from 0.6 µg/kg/2 weeks in our study and followed the dosing protocol.

The median time to response for CERA (10 weeks) in our study was although similar to that reported in previous studies of patients with CKD receiving darbepoetin alfa or epoetin. Coyne et al reported a median time to response of 10 weeks (range, 1 to 20 weeks) for darbepoetin alfa and 8 weeks (range, 3 to 20 weeks) for epoetin in a cohort of patients with CKD on dialysis.[77]

It is worth noting that our epoetin response rate was greater than that reported in a 20-week study in which darbepoetin alfa (0.45mcg/kg once weekly) achieved a 72% (95% CI, 62 to 81) response rate compared with 84% (95% CI, 66 to 95) for epoetin alfa (50 IU/kg 3 times weekly).[77]

There was a significant increase in mean Hb from baseline to the end of treatment period (24 weeks) in our study by 2.28 g/ dL ± 1.37 g/dL and 2.43 ± 1.29 g/dL in the CERA and erythropoietin groups respectively. These findings are in line with the AMICUS study where mean changes in Hb levels from baseline to end of correction period of 24 weeks was 2.70 ± 1.45 g/dL and 2.56 ± 1.31 g/dL with CERA and epoetin, respectively. Similar results were found in an Indian study done by Georgy K Nainan et al on 189 patients on dialysis, having Haemoglobin between 8 – 10 g/dL and not receiving any ESA for last 8 weeks from 14 dialysis centers across India. CERA was given intravenously (IV) at the dose of 0.6 µg/kg every two weeks. Mean change of Hb from baseline to end of 16 weeks was 2.11 ± 1.37 g/dL and 2.08 ± 1.29 g/dL in intent to treat (ITT) and per

protocol (PP) population respectively. Mean time to achieve Hb response was 6.10 ± 3.87 weeks and 6.16 ± 3.92 weeks in ITT and PP populations respectively.[73]

Median dose at the time of Hb response went up to 1.05 µg/kg/2 weeks. After the first month there was a sharp increase in CERA dose by 33% in response to minimal increase of Hb level. The clinical studies of CERA have shown a dose-dependent erythropoietic response. In two phase II studies, serum concentrations of CERA were positively correlated with Hb response.[78,79] These studies also showed a trend towards more rapid Hb response evident with higher dose.

Another potential reason for less Hb response rate and delayed time to response in the CERA group was iron supplementation. Baseline median transferring saturation and ferritin levels were 37% and 611.5 ng/ml respectively in CERA group. After the patients were administered study drug, median TSAT declined to 33% and median ferritin dropped to 541 ng/mL at weeks 6 and 18 respectively in CERA group. During the correction phase most patients had taken oral iron supplementation. IV iron treatments were intermittently prescribed to maintaine iron indices in prescribed range. Iron is essential to support erythropoiesis. Although EPO treatment is greatly effective in correcting Hb levels, absolute or functional iron deficiency causes a state of hypo responsiveness to EPOs. Baseline iron parameters in our study were definitely in target range as recommended by current guidelines, but iron levels decreased due to rapid consumption with initiation of EPO treatment. While most of the patients maintained tsat of >30% and serum ferritin of > 500 ng/mL during the correction phase, there were some proportion of patients in iron deficiency, especially during the first 12 weeks in CERA group. It might partially contribute to high dose of study drugs at the time of Hb response.

Similarly low proportions of patients required RBC transfusions during the correction period ,8% in CERA, 10% in epoetin beta group. This difference was statistically not significant (p value >0.05), further indicating that

C.E.R.A once every 2 weeks was as effective as epoetin beta for the correction of anemia.

In another important finding, the diabetic patients in our study had poor Hb response to therapy (EPO/CERA) as compared to non-diabetic patients. Argiris Symeonidis et al found that diabetic patients had significantly lower serum Epo levels as compared to non-diabetics (36.5+/-61 vs 69.4+/-191 IU/ml, $p<0.0001$), and this was true for all etiologic groups of anemia with the exception of patients with myeloproliferative disorders and those with megaloblastic anemia. Inappropriately low serum EPO level is a uniform feature in patients with type II diabetes mellitus and may represent a constitutive blunted response to anemia or an altered metabolic rate of EPO, probably as a result of abnormal glycosylation of the cytokine.[80] Georg Biesenbach et al conducted a study to evaluate the differences in hemoglobin response to erythropoietin in diabetic and non-diabetic patients on chronic hemodialysis. He found that the mean Hb level increased more, but not significantly, in non-diabetic patients than in diabetic patients. After 6 months the actual EPO requirement was higher in diabetic than in non-diabetic subjects (244+/-122 versus 183+/-118 IU/kg/week; $p<0.05$).[81]

The most common adverse event (AE) during the study was worsening of hypertension; 26% in CERA group and 16% in EPO group (difference was statistically insignificant). This was also seen in patients receiving CERA in ARCTOS trial [76] and it is due to impairment of both the endothelium dependent as well as endothelium-independent vasodilatation.[82] Sameer G. Vankar et al also reported worsening of BP as the most commonly reported adverse event which was seen among 42.9 per cent patients (n= 15) of Diabetic CKD receiving CERA who were not on dialysis.[60] Valeria M Saglimbene et al also concluded in his meta analysis that there was evidence that CERA had little or no effects on mortality (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65), major adverse cardiovascular events (RR 5.09, 95% CI 0.25 to 105.23; RR 5.56, 95% CI 0.99 to 31.30),

hypertension (RR 1.01, 95% CI 0.75 to 1.37; RR 1.00, 95% CI 0.79 to 1.28), need for blood transfusion (RR 1.02, 95% CI 0.72 to 1.46; RR 0.94, 95% CI 0.55 to 1.61), or additional iron therapy (RR 1.03, 95% CI 0.91 to 1.15; RR 0.99, 95% CI 0.95 to 1.03) compared to epoetin alfa/beta or darbepoetin alfa respectively.[59]

Mortality of 4.23% in our study is higher than the deaths reported in the AMICUS study (1.5%). This may be because of slightly higher mean age of the study population which was 55.36 years and 58.48 years in CERA and EPO group respectively in our study as compared to AMICUS. The age of our population was higher than the reported mean age of patients with ESRD in India. Many studies have reported mean age of patients of ESRD in India. Michael P. Hezel[83] has reported that mean age of patients with ESRD in India is in between 32-42 years. Sakhuja and Sud et al[84] have reported mean age of 42 years at the time of detection of ESRD in India.

None of the deaths or severe AEs reported in our study were considered to be related to study medication as per investigator's judgment and all deaths were attributed to underlying or co-morbid disorders. Gidithi s et al[85] studied demographics and clinical data of Indian patients on haemodialysis at a tertiary care centre. They reported 15.1% deaths during first 90 days of initiation of haemodialysis and 17.1% during three year period. They have attributed causes of death to ischaemic heart disease, stroke, pneumonia, sepsis and catheter related infection. Co-morbidities play important role in mortality in haemodialysis patients. Because CKD prevalence is predicted to increase, largely because of the aging population and the increasing prevalence of type 2 diabetes, anemia treatment will place additional pressure on already hard pressed renal units. Baseline characteristics, causes of CKD, and type and distribution of co-morbidities show that our study population is typical of patients seen in routine nephrology practice.

We acknowledge certain limitations of this study. Firstly, the open-label study design may have had an impact on the data, such as incidence and severity of any AEs. Secondly, the peritoneal dialysis population was not included. Thirdly, the study was for a short duration and the sample size was small. Fourthly, the improvement in the quality of life (QoL) score was not assessed and also the effect of the treatment on the major and the minor chronic complications of diabetes mellitus was also not assessed. Also, the erythropoietin antibody testing was not performed during the study and only descriptive statistics were used.

In summary, our results show that CERA once every 2 weeks is as effective and well tolerated as more frequent (3 times per week) epoetin with predictable and controlled correction of anemia. Although, time to hemoglobin response was longer in CERA group as compared to EPO group. This must be kept in mind while converting twice per month CERA to once per month maintenance CERA therapy. These features have the potential to provide advancement in the management of anemia by minimizing renal unit workload during the correction of anemia.

SUMMARY AND CONCLUSION

1. This was an open-label, single center, randomized, parallel-group study, conducted in patients undergoing maintenance hemodialysis at DMCH Dialysis centre from May 2020– May 2021.
2. 100 patients on maintenance dialysis were included in the study and were randomized into two groups (50 patients each), one receiving conventional Erythropoietin alfa/beta IV three times a week and the other receiving CERA once in two weeks. The study population was followed up for 24 weeks.
3. Mean age was 58.48±13.42 years in EPO group and 55.36±8.54 in CERA group**.** Most of the patients (52% in EPO group and 70% in CERA group) belonged to the age group of 41-60.
4. Mean BMI (Kg/m^2) was 21.18±1.49 in EPO group and 21.83±2.23 in CERA group. There were no obese patients in the study. Majority of the patients having BMI of < 23 Kg/m^2.
5. Male preponderance was seen in both the groups, 36(72%) in EPO group and 33(66%) in CERA group.
6. Among Basic disease, Diabetic kidney disease was the most common with 21(42%) patients in EPO group and 18(36%) patients in CERA group, followed by Hypertensive nephrosclerosis with 10(20%) patients in EPO and 10(20%) patients in CERA group. 11 patients (22%) in EPO group and 7 patients(14%) in CERA group had CGN as the cause for CKD, which was the third most common cause in our study population.
7. Mean dialysis vintage was 23.66 ± 11.74 weeks in EPO group and 24.06 ± 10.70 weeks in CERA group. Most of the patients had dialysis vintage between 24-48 weeks. Median dialysis vintage was 22 weeks in EPO group and 24 weeks in CERA group.
8. Dialysis adequacy was maintained throughout the study with mean kt/v of 1.45 in EPO group and 1.44 in CERA group.

9. The Hemoglobin response rate was similar in both EPO and CERA groups after 24 weeks correction period.
10. Time to Hemoglobin response was longer in CERA group as Compared to EPO group. This must be kept in mind while converting twice per month CERA to once per month maintenance CERA therapy.
11. Requirement of Blood transfusions were similar in both CERA and EPO groups.
12. Overall Hemoglobin response rates were poorer in diabetic as compared to non-diabetic population in both CERA and EPO groups.
13. Hemoglobin response rates were poor in diabetic patients receiving CERA as compared to EPO.
14. Time to Hemoglobin response was similar in diabetic and non-diabetic populations.
15. Higher incidence of worsening of blood pressure were seen in CERA group as compared to EPO group but overall difference in adverse events was insignificant. It is hence advised to monitor blood pressure closely while administering CERA.

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			EPO GROUP																							
SR. No.	PATIENT INITIALS	MRD No	AGE	SEX	WEIGHT	BMI (kg/m2)	BASIC DISEASE & COMORBIDITIES			dialysis vintage (weeks)	kt/v	Hb (week)														
							HTN	DM	OTHER			0	2	4	6	8	10	12	14	16	18	20	22	24	0 week
1	C.L	740445	47	MALE	63	21.6	YES	NO	NEPHROLITHIASIS	40	1.57	8.6	8.3	7.8	8.5	9.5	9.6	10.1	10.2	9.7	9.9	10.6	11	10.8	40
2	J.S	398147	64	FEMALE	62	23.3	YES	NO	CGN	24	1.23	8.2	7.6	7.1	7.5	7.3	7.8	8	9.5	8.6	8.8	9	9	8.9	40
3	A.S	111923	79	MALE	68	20.9	YES	YES	CAD CVA	12	1.17	8.1	8.3	8.6	9.1	9.3	9.6	9.9	10.2	10.5	10.6	11	10.8	11.2	40
4	T.K	24867	50	FEMALE	70	22.3	YES	NO	OLD CVA CIN	32	1.67	8.8	8.7	8.9	9	8.9	9.2	9.1	9.4	9	8.9	9.2	9.5	9.6	40
5	H.K	934199	46	MALE	46	19.1	YES	NO	AMYLOIDOSIS	24	1.88	8.3	8.4	8.3	8.7	9.2	9.6	9.5	9.6	9.9	10.1	9.9	10.3	10.1	40
6	H.S	688358	63	FEMALE	64	20.4	YES	YES		48	1.46	8.8	8.5	9.1	9.6	10.2	10.5	10.1	10.5	10.6	10.7	11.1	11.3	11.8	40
7	K.L	632497	59	MALE	62	19.8	YES	YES		8	1.93	8.8	9.2	9.9	10.5	10.9	11.2	11.9	12.3	11.7	11.5	10.7	10.9	11.6	40
8	H.S	942022	58	MALE	58	17.8	YES	NO	CAD	12	1.43	8.5	8.3	8.6	8.7	8.9	9.2	9	9.1	9.5	9.6	10.2	10.5	10.2	40
9	A.D	1030348	58	MALE	62	20.8	YES	YES		6	1.38	8	8	7.8	8.1	8.3	8.6	8.3	8.5	8.3	8.6	8.7	NA	NA	40
10	M.C	21107	89	MALE	60	19.1	YES	NO		18	1.2	8.2	7.6	7.9	8.5	9.3	9.5	9.8	9.5	10.1	10.2	9.9	10.1	10.2	40
11	M.R	181736	81	MALE	71	21.6	YES	NO	CVA CGN	32	1.27	9	8.8	9.5	9.9	10.2	10.5	10.8	11	11.3	11.7	12.1	12.4	12	40
12	J.K	833683	53	MALE	64	22	YES	NO	CGN	24	1.31	8.5	8.1	8.9	9.6	9.8	9.5	10.1	10	9.8	10.2	10.6	10.3	10.5	40
13	A.K	652368	60	MALE	60	23	YES	NO	CGN	12	1.18	9	8.6	8.9	9.3	9.8	10.2	10.5	10.6	11.2	11	10.8	11.1	10.9	40
14	G.S	1048112	70	FEMALE	65	22.3	NO	NO	MULTIPLE MYELOMA CAST NEPHROPATHY HYPOTHY	26	1.32	8	8.2	8.6	9.2	9.3	9.4	9.2	9.8	10.2	10.5	10.7	11	11.3	40
15	R.K	554873	55	MALE	64	21.8	YES	YES		8	1.64	8.9	9.3	9.8	10.2	10.6	10.8	11.3	11.9	11.5	11.8	12.2	11	11.5	40
16	K.S	925413	48	MALE	64	22	NO	YES	CAD	24	1.58	8.9	8.8	8.9	9.7	9.5	10.2	11.1	11.3	10.1	10.2	10.7	10.3	11	40
17	R.S	562915	52	MALE	68	23.2	YES	NO		54	1.45	8.3	7.6	8.1	8.9	9.5	9.6	9.2	9.2	9.5	9.6	9.6	10.1	9.8	40
18	M.D	47785	71	FEMALE	56	21	YES	YES	CVA CAD BPH	32	1.69	8.3	8.6	8.9	9.2	9.8	10.2	10.5	10.7	11	11.4	11.8	12.2	12.5	40
19	B.S	29653	60	MALE	71	23.4	YES	YES		18	1.34	8.6	8.8	9.1	9.8	10.2	11.2	10.2	10.6	11.3	11.5	10.8	11	11.2	40
20	D.P	124566	37	MALE	64	20.7	NO	YES		16	1.43	8.3	8.2	8.5	8.6	8.2	8.8	9.2	9.6	9.8	9.6	10.1	10.9	10.6	40
21	J.S	1192678	65	MALE	60	20.6	YES	YES		24	1.55	8.4	8.5	8.7	8.9	9	8.8	9.3	9.5	9.2	9.4	9	9.4	9.5	40
22	H.P.S	810367	59	MALE	56	19.6	YES	YES	CAD LV DYSFUNCTION	18	1.59	8	8.9	9.2	9.8	11.5	12.3	11.8	12	10.6	11.5	12.3	11.2	11.5	40
23	S.K	414306	34	FEMALE	59	22.2	NO	NO	CGN	24	1.66	8.6	8.9	9.2	9.8	9.5	10.1	10.3	10.5	11	10.8	11.3	11.5	12.2	40
24	B.R.S	26218	64	FEMALE	64	20.3	YES	NO	CAD	12	1.72	8.8	8.7	9.4	9.8	10.1	10.2	10.5	10	11.1	11.5	11	10.6	10.8	40
25	A.S	769542	31	FEMALE	48	19.5	YES	NO	CGN	22	1.82	8.8	9.1	9.6	9.9	10	10.5	10.3	10.9	11.3	11.5	NA	NA	NA	40
26	S.S	404689	66	MALE	68	23.5	NO	YES	CAD	16	1.24	8.3	8.1	8.5	8.7	9.3	9.1	9.5	NA	NA	NA	NA	NA	NA	40
27	H.L.B	614324	75	MALE	75	19.8	YES	YES		24	1.19	8.6	8.3	8.7	9.2	9.7	10.2	10.1	10.6	10.9	11.3	11.6	12.1	11.7	40
28	S.R	460901	56	FEMALE	54	20.1	YES	NO		22	1.32	8	7.6	7.9	8.4	8.7	9.2	9.6	9.9	10.1	9.9	10	10.4	10.6	40
29	F.C	260418	56	MALE	68	21.8	YES	NO	NEPHROLITHIASIS	12	1.28	8.4	8.3	8.8	9.2	9.6	9.3	9.9	10.2	10.4	10.7	10.4	11.1	11.4	40
30	C.H	731016	34	MALE	87	22.5	YES	NO	CGN	24	1.51	8.7	9	9.3	9.1	9.5	9.8	10.2	10.6	10.6	11.3	11.6	12.1	12.3	40
31	V.C	239809	89	MALE	60	19.1	YES	NO		18	1.5	8.2	7.6	7.9	8.5	9.3	9.5	9.8	9.5	10.1	10.2	9.9	10.1	10.2	40
32	K.C	639772	81	MALE	71	21.6	YES	NO	CVA CGN	18	1.62	9	8.8	9.5	9.9	10.2	10.5	10.3	10.8	10.6	11	10.8	10.3	10.2	40
33	S.K	652368	53	MALE	64	22	YES	NO		24	1.68	8.5	8.1	8.9	9.6	9.8	9.5	10.1	10	9.8	10.2	10.6	10.3	10.5	40
34	B.B	482210	60	MALE	60	23	YES	NO	CGN	18	1.49	9	8.6	8.9	9.3	9.8	10.2	10.5	10.6	11.2	11.5	11.8	12.1	11.9	40
35	N.D	263321	70	FEMALE	65	22.3	NO	NO	MULTIPLE MYELOMA CAST NEPHROPATHY HYPOTHY	16	1.34	8	8.2	8.6	9.2	9.3	9.4	9.2	9.8	10.2	10.5	10.7	11	11.3	40
36	L.S	1006690	55	MALE	64	21.8	YES	YES		38	1.24	8.9	9.3	9.8	10.2	10.6	10.8	11.3	11.5	11.8	12.2	12.5	12	11.8	40
37	M.S	934199	48	MALE	64	22	NO	YES	CAD	12	1.67	8.5	8.8	8.9	9.7	9.5	10.2	11.1	11.3	10.1	10.2	10.7	10.3	11	40
38	M.S	447350	52	MALE	68	23.2	YES	NO		18	1.31	8.3	7.6	8.1	8.9	9.5	9.6	9.2	9.2	9.5	9.6	9.6	10.1	9.8	40
39	S.K	925412	71	FEMALE	56	21	YES	YES	CVA CAD	40	1.59	8.3	8.6	8.9	9.2	9.8	10.2	10.5	10.5	11.5	11.8	11.8	11.6	12	40
40	H.S	407540	60	MALE	71	23.4	YES	YES		18	1.53	8.4	8.8	9.1	9.8	10.2	11.2	10.2	10.6	11.3	11.5	10.8	11	11.2	40
41	A.S	124566	37	MALE	64	20.7	NO	YES		12	1.57	8.3	8.2	8.5	8.6	8.2	8.8	9.2	9.6	9.8	9.6	10.1	10.9	10.6	40
42	R.S	95232	65	MALE	60	20.6	YES	YES		24	1.48	8.8	8.7	8.5	8.8	9	9.2	8.9	9.4	9.2	8.9	9.2	9.4	9.6	40
43	D.K	592269	59	MALE	56	19.6	YES	YES	CAD LV DYSFUNCTION	18	1.32	8	8.9	9.2	9.8	11.5	12.3	11.8	12	10.6	11.5	12.3	11.2	11.5	40
44	R.R	279482	34	FEMALE	59	22.2	NO	NO	CGN	36	1.49	8.6	8.9	9.2	9.8	9.5	10.1	10.3	10.5	11	10.8	11.3	11.5	12.2	40
45	T.D	898013	64	FEMALE	64	20.3	YES	NO	CAD	44	1.28	8.8	8.7	9.4	9.8	10.1	10.2	10.5	10	11.1	11.5	11	10.6	10.8	40
46	B.B	400614	46	MALE	46	19.1	YES	NO	ANTI GBM	24	1.29	8.3	8.4	8.3	8.7	9.2	9.6	9.5	9.6	9.9	10.1	9.9	10.3	10.1	40
47	J.K	174141	63	FEMALE	64	20.4	YES	YES		36	1.2	8.8	8.5	9.1	9.6	10.2	10.5	10.1	10.5	10.6	10.7	11.1	11.3	11.8	40
48	N.S	1191632	59	MALE	62	19.8	YES	YES		21	1.21	8.8	9.2	9.9	10.5	10.9	11.2	11.9	12.3	11,7	11.5	10.7	10.9	11.6	40
49	S.N.V	940113	58	MALE	58	17.8	YES	NO	CAD	20	1.19	8.5	8.3	8.6	8.7	8.9	9.2	9	9.1	9.5	9.6	10.2	10.5	10.2	40
50	A.A	657597	60	MALE	60	23	YES	NO	CGN/CAD	60	1.5	9	8.6	8.9	9.3	9.8	10.2	10.5	10.6	11.2	11	10.8	11.1	10.9	40

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SR. No.	PATIENT INITIALS	MRD No	ERYTHROPOETIN DOSE (IU/KG)/ (mcg/KG)						blood transfusion (y/n)	hb response (y/n)	time to hb response (week)	tsat(%) (week)					ferritin (week)					B12	FOLATE	CRP	ADVERSE EVENTS	DEATH
			4 week	8 week	12 week	16 week	20 week	24 week				0	6	12	18	24	0	6	12	18	24					
1	C.L	740445	60	75	75	75	75	75	NO	YES	10	46.7	32	36.5	46.3	44.4	630	516	560	480	550	>2000	5.6	1.2		
2	J.S	398147	60	80	80	80	80	80	YES	NO	NA	30	30.7	33.4	27.7	25	518	583	475	512	532	>1000	4.8	5.8	NEED FOR BT	
3	A.S	111923	50	50	50	50	50	50	NO	YES	6	40.7	47.9	38.3	37.7	38.5	796	680	592	630	612	982	8.6	2.6		
4	T.K	24867	50	60	60	60	60	60	NO	NO	NA	28.8	50	38.2	39.6	38.8	702	621	582	608	530	>1500	6.8	1.3		
5	H.K	934199	50	60	60	60	60	60	NO	YES	10	31.1	49.4	39.7	38.8	40	792	680	623	670	720	>1500	8.9	1.2		
6	H.S	688358	40	40	40	40	40	40	NO	YES	8	31.6	36	39	43	42	514	584	568	584	596	>1000	5.4	6.1		
7	K.L	632497	40	40	40	40	40	40	NO	YES	4	35.4	37	34	32	35	638	712	683	690	564	>1000	8.4	2.1		
8	H.S	942022	50	60	60	60	60	60	NO	YES	16	25	31.5	37	46.2	48.4	670	360	580	510	590	>2000	6.8	1.6	HIGH BP,CAD	
9	A.D	1030348	60	75	75	75	75	NA	NO	NO	NA	22	34	38	37.3	NA	618	720	653	701	NA	1200	8.1	5.9	GI BLEED	Y
10	M.C	21107	60	60	60	60	60	60	NO	YES	8	35.2	37.2	34.8	30	29.6	610	712	510	498	523	910	8.7	5.6		
11	M.R	181736	50	60	60	60	60	60	NO	YES	8	49.2	40.3	39	39.4	39.5	630	580	710	621	539	1200	7.2	8.1		
12	J.K	833683	50	50	50	50	50	50	NO	YES	6	35.4	37.1	33.6	38.6	41.7	680	710	593	564	601	1280	8.9	3.2		
13	A.K	652368	60	75	75	75	75	75	NO	YES	10	33.9	33.8	39	36	35.4	638	721	656	583	672	>2000	8.2	1.1	HIGH BP	
14	G.S	1048112	50	50	50	50	50	50	NO	YES	6	33	29	37	34	36	2000	810	930	1333	1210	230	4.5	2.8		
15	R.K	554873	40	50	50	50	50	50	NO	YES	6	35.4	34	31	34	32	523	710	690	564	623	780	10.2	4.8		
16	K.S	925413	40	50	50	50	50	50	NO	YES	10	32.8	39	31.7	27.1	30.2	621	582	492	501	563	1200	9.1	5.3		
17	R.S	562915	50	50	50	50	50	50	NO	YES	8	32.5	37.5	32.8	30	42	610	512	468	550	510	>2000	10.8	2.4		
18	M.D	47785	50	50	50	50	50	50	NO	YES	8	32	35	42..1	55.2	38.6	582	512	580	608	550	1002	10.2	1.2		
19	B.S	29653	50	50	50	50	50	50	NO	YES	6	40	41	37	37	37.1	700	631	538	610	589	>2000	5.8	1.2		
20	D.P	124566	50	75	75	75	75	75	NO	YES	14	39	47	36	38.8	41.7	630	592	690	740	721	>1200	8.9	2.3		
21	J.S	1192678	60	75	75	75	75	75	NO	NO	NA	38	41.6	46.9	37.1	37.8	710	638	521	630	589	816	7.9	2.3		
22	H.P.S	810367	40	40	40	40	40	40	YES	YES	4	55	59	49	50.4	35.6	628	512	410	318	490	>2000	6.8	0.6	NEED FOR BT	
23	S.K	414306	50	50	50	50	50	50	NO	YES	6	55	56.9	53	50.4	35	620	520	410	320	420	982	10.2	3.6		
24	B.R.S	26218	50	50	50	50	50	50	NO	YES	6	32.6	51	54	54	31.8	512	560	584	561	544	1221	12.4	5		
25	A.S	769542	50	50	50	50	NA	NA	NO	YES	6	27.2	38.6	36.1	25	NA	612	709	632	482	NA	1090	6.8	5.34	HIGH BP	YES-CARDIAC ARREST
26	S.S	404689	50	50	50	NA	NA	NA	NO	YES	8	45.7	30.5	38.1	NA	NA	509	450	599	NA	NA	1800	7.3	2.1	HIGH BP	YES
27	H.L.B	614324	60	60	60	60	60	60	NO	YES	8	55	38.9	49.3	58	64.5	648	672	760	900	783	1000	6.7	2.5		
28	S.R	460901	60	75	75	75	75	75	NO	YES	10	32.6	21.9	28.9	35	30.6	406	530	489	501	540	1100	4.8	2.6		
29	F.C	260418	50	50	50	50	50	50	NO	YES	8	46.8	57.4	43.7	39.2	40.8	679	688	739	523	698	980	6.8	1.1		
30	C.H	731016	50	60	60	60	60	60	NO	YES	10	56.4	54.4	40.3	55.3	48.1	590	539	610	622	597	893	9.2	1.6	HIGH BP RECORDS	
31	V.C	239809	60	60	60	60	60	60	NO	YES	8	35.2	37.2	34.8	30	29.6	610	712	510	498	523	910	8.7	5.6		
32	K.C	639772	50	50	50	50	50	50	NO	YES	8	49.2	40.3	39	39.4	39.5	630	580	710	621	539	1200	7.2	8.1		
33	S.K	652368	50	50	50	50	50	50	NO	YES	6	35.4	37.1	33.6	38.6	41.7	680	710	593	564	601	1280	8.9	3.2		
34	B.B	482210	50	60	60	60	60	60	NO	YES	10	33.9	33.8	39	36	35.4	638	721	656	583	672	>2000	8.2	1.1	HIGH BP	
35	N.D	263321	50	50	50	50	50	50	NO	YES	6	33	29	37	34	36	2000	810	930	1333	1210	230	4.5	2.8		
36	L.S	1006690	50	50	50	50	50	50	YES	YES	6	35.4	34	31	34	32	523	710	690	564	623	780	10.2	4.8	NEED FOR BT	
37	M.S	934199	40	50	50	50	50	50	NO	YES	10	32.8	39	31.7	27.1	30.2	621	582	492	501	563	1200	9.1	5.3		
38	M.S	447350	60	60	60	60	60	60	NO	YES	8	32.5	37.5	32.8	30	42	610	512	468	550	510	>2000	10.8	2.4		
39	S.K	925412	50	50	50	50	50	50	NO	YES	8	32	35	42..1	55.2	38.6	582	512	580	608	550	1002	10.2	1.2		
40	H.S	407540	50	50	50	50	50	50	NO	YES	6	40	41	37	37	37.1	700	631	538	610	589	>2000	5.8	1.2		
41	A.S	124566	50	75	75	75	75	75	NO	YES	14	39	47	36	38.8	41.7	630	592	690	740	721	>1200	8.9	2.3		
42	R.S	95232	60	75	75	75	75	75	NO	NO	NA	38	41.6	46.9	37.1	37.8	710	638	521	630	589	816	7.9	2.3		
43	D.K	592269	40	40	40	40	40	40	YES	YES	4	55	59	49	50.4	35.6	628	512	410	318	490	>2000	6.8	0.6	NEED FOR BT	
44	R.R	279482	50	50	50	50	50	50	NO	YES	6	55	56.9	53	50.4	35	620	520	410	320	420	982	10.2	3.6		
45	T.D	898013	50	50	50	50	50	50	NO	YES	6	32.6	51	54	54	31.8	512	560	584	561	544	1221	12.4	5		
46	B.B	400614	50	60	60	60	60	60	NO	YES	10	31.1	49.4	39.7	38.8	40	792	680	623	670	720	>1500	8.9	1.2		
47	J.K	174141	50	50	50	50	50	50	NO	YES	8	31.6	36	39	43	42	514	584	568	584	596	>1000	5.4	6.1		
48	N.S	1191632	40	40	40	40	40	40	NO	YES	4	35.4	37	34	32	35	638	712	683	690	564	>1000	8.4	2.1		
49	S.N.V	940113	50	60	60	60	60	60	NO	YES	16	25	31.5	37	46.2	48.4	670	360	580	510	590	>2000	6.8	1.6	HIGH BP,CAD	
50	A.A	657597	50	60	60	60	60	60	NO	YES	10	33.9	33.8	39	36	35.4	638	721	656	583	672	>2000	8.2	1.1	HIGH BP	

			CERA GROUP																							
SR. No.	PATIENT INITIALS	MRD No	AGE	SEX	WEIGHT	BMI (kg/m2)	BASIC DISEASE & COMORBIDITIES			dialysis vintage (weeks)	kt/v	Hb (week)														
							HTN	DM	OTHER			0	2	4	6	8	10	12	14	16	18	20	22	24	0 week
1	J.S	93483	54	MALE	64	22	YES	YES	CAD	32	1.67	8.7	8.5	8.1	8.3	8.9	9.5	9.8	9.8	10.2	10.6	9.8	11.2	10.8	0.6
2	R.S	860109	60	MALE	68	21.8	YES	YES	NEPHROLITHIASIS	48	1.22	8.3	7.9	7.6	7.8	8	8.2	8	8.2	7.9	9.1	9.3	8.8	9.3	0.6
3	M.S	921456	63	MALE	68	22.6	YES	YES		24	1.65	8.7	8.5	8.3	8.3	8.4	8.1	8	8.3	8.2	8.4	8.5	8.5	8.2	0.6
4	H.L	945467	56	MALE	62	21	YES	YES	CAD	15	1.28	8.3	8.5	8.5	8.8	9.1	9.5	9.3	9.6	10.1	10.8	11.3	10.9	11.8	0.6
5	D.S	154306	33	FEMALE	82	26.4	YES	YES	NEPHROLITHIASIS	24	1.44	8.5	7.8	8	8.2	8	8.1	8.3	8.1	8	8.3	8.4	8.1	8.4	0.6
6	C.S	243503	48	FEMALE	68	22.2	YES	YES	NEPHROLITHIASIS	36	1.29	8.1	8.5	8.4	9	9.4	10.1	10.5	11.5	11.4	11.8	11.6	12	11.2	0.6
7	G.S	1006804	47	MALE	65	21	NO	NO	BPH	14	1.54	8.2	8.7	8.8	9.2	9.8	10.1	9.6	10.5	10.8	10.5	10.4	11.2	11	0.6
8	L.K	419328	58	FEMALE	68	24.7	NO	NO		24	1.43	8.3	8	8.5	9.1	9.5	10.1	10.6	11.2	11.8	12.5	11.9	11.6	12	0.6
9	H.K	925412	64	FEMALE	68	21	YES	NO		8	1.38	8.2	8.3	7.9	7.9	8.5	8.8	9.1	8.9	9.5	10.2	9.9	10.5	10.6	0.6
10	K.R	716342	47	MALE	58	21.3	NO	NO	CAD	36	1.48	8.6	8.1	7.8	7.4	8.7	9.3	9.8	9.7	10.2	10.9	11.5	11	11.3	0.6
11	M.L.C	317434	67	MALE	62	21.8	YES	NO	COPD/ ANCA	28	1.27	8.4	8.6	9.3	9.9	10.5	10.8	11.3	11.7	12.3	12.6	11.5	11.7	11.3	0.6
12	D.A	234168	47	MALE	56	20.3	YES	NO	CGN	21	1.31	9.2	8.9	8.6	9.2	9.5	10.2	10.5	10.3	10.6	10.5	11.5	11.2	11.2	0.6
13	K.K	34714	64	MALE	80	24.3	YES	YES	CAD	18	1.58	8.4	8.6	8.5	8.9	9.2	9.8	10.5	10.9	11.2	11.8	12.3	11.9	11.6	0.6
14	R.V	942022	57	MALE	84	24.5	YES	YES		10	1.38	8.1	7.8	8	8.5	9.1	9.6	10.2	9.6	11.3	11.6	10.8	10.6	10.8	0.6
15	S.K	93483	58	MALE	54	16.8	YES	YES		36	1.65	8.1	7.6	7.9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.6
16	R.S	667922	55	MALE	67	23.2	YES	YES		8	1.55	8.2	7.8	7.1	8	7.9	8.1	8	7.8	7.9	8.1	8	7.9	8.1	0.6
17	M.R	140640	59	FEMALE	63	25.2	YES	YES		40	1.47	8.2	7.7	8.1	8.6	8.8	9.5	9.1	9.3	9.6	10.1	9.8	9.7	10.2	0.6
18	H.S	552121	44	FEMALE	60	21.3	YES	YES	CGN	32	1.22	8.6	8	7.8	7.9	8	8.1	8.3	8.1	8.4	8.5	8.2	8.4	8.1	0.6
19	D.K	341389	55	FEMALE	50	20.6	YES	YES	CIN	24	1.34	8.5	8.8	9.2	9.4	9.8	10.1	10.5	11.1	11	11.6	11.2	10.9	11.2	0.6
20	G.S	137314	57	MALE	68	23.6	YES	NO	CGN	12	1.43	8.6	8.3	8.1	8.7	9.3	9.5	9.6	10.2	10.1	11	10.8	11.2	11.3	0.6
21	K.K	494453	41	MALE	60	19.6	YES	YES	CLD	16	1.55	8.1	7	7.9	8.2	8.8	8.9	9.3	9.5	9.9	10.2	9.9	9.5	10.2	0.6
22	R.G	1217297	61	MALE	68	22.5	YES	NO		12	1.59	8.5	8.1	8.7	9.2	9.6	9.9	9.8	10.3	11.2	11	11.5	11.1	10.8	0.6
23	M.S	70714	59	MALE	64	20.2	YES	NO		24	1.21	8.5	8.2	8.6	8.7	8.9	9.6	9.2	9.7	9.5	9.6	10.2	10.5	10.2	0.6
24	H.S	900038	70	MALE	62	18.7	YES	NO		56	1.54	8.5	8.1	8.2	8.6	9.2	9.8	9.5	10.5	11.5	11.3	11.2	12.6	11.7	0.6
25	K.B	469758	66	FEMALE	65	20.1	YES	YES	VUR	32	1.82	8.5	7.6	7.8	8.2	8.5	9	9.6	9.9	10.4	10.9	11.3	11.6	11.5	0.6
26	V.K.G	375319	54	MALE	64	22	YES	YES	CAD	32	1.24	8.7	8.5	8.1	8.3	8.9	9.5	9.8	9.8	10.2	10.6	NA	NA	NA	0.6
27	S.K	974111	60	MALE	68	21.8	NO	YES	NEPHROLITHIASIS	24	1.94	8.3	7.9	8.2	7.2	7.2	9.4	9.8	9	8.9	9.1	9.3	8.8	9.3	0.6
28	B.K	249918	63	FEMALE	69	19.7	YES	NO		12	1.32	8.4	7.8	8.4	8.3	8.6	8.9	9.2	9.2	9.8	10.4	10.6	10.8	10.6	0.6
29	G.J	989542	55	FEMALE	50	20.6	YES	NO	CIN	24	1.28	8.5	8.8	9.2	9.4	9.8	10.1	10.5	11.1	11	11.6	11.2	10.9	11.2	0.6
30	B.K	52239	57	MALE	68	23.6	YES	NO	CGN	26	1.51	8.6	8.3	8.1	8.7	9.3	9.5	9.6	10.2	10.1	11	10.8	11.2	11.3	0.6
31	J.S	1195868	41	MALE	60	19.6	YES	NO	CLD	18	1.5	8.1	7	7.9	8.2	8.8	8.9	9.3	9.5	9.9	10.2	9.9	9.5	10.2	0.6
32	H.S	626595	61	MALE	68	22.5	YES	NO		22	1.62	8.5	8.1	8.7	9.2	9.6	9.9	9.8	10.3	11.2	11	11.5	11.1	10.8	0.6
33	A.K	1010678	59	MALE	64	20.2	YES	NO		24	1.23	8.5	8.2	8.6	8.7	8.9	9.6	9.2	9.7	9.5	9.6	10.2	10.5	10.2	0.6
34	A.S	1030379	33	FEMALE	82	26.4	YES	NO	NEPHROLITHIASIS	16	1.49	8.5	7.8	8.5	9.1	9.8	10.2	10.5	10.7	10.9	11.1	11.3	11.5	11.9	0.6
35	C.L	1244466	48	FEMALE	68	22.2	YES	YES	NEPHROLITHIASIS	18	1.5	8.1	8.5	8.4	9	9.4	10.1	10.5	11.5	11.4	11.8	11.6	12	11.2	0.6
36	T.C	1203171	47	MALE	65	21	YES	YES		8	1.34	8.2	7.8	7.5	7.7	7.9	7.8	8.1	8	7.9	7.6	7.8	7.9	8	0.6
37	A.D	120405	58	FEMALE	68	24.7	YES	NO		12	1.55	8.3	8	8.5	9.1	9.5	10.1	10.6	11.2	11.8	12.5	11.9	11.6	12	0.6
38	G.K	667408	64	FEMALE	68	21	YES	NO		36	1.4	8.2	8.3	7.9	7.9	8.5	8.8	9.1	8.9	9.5	10.2	9.9	10.5	10.6	0.6
39	A.C	266575	47	MALE	58	21.3	YES	YES	CAD	32	1.32	8.6	8.1	7.8	7.4	8.7	9.3	9.8	9.7	10.2	10.9	11.5	11	11.3	0.6
40	D.P.G	1017709	67	MALE	62	21.8	YES	NO	ANCA	12	1.59	8.5	8.6	9.3	9.9	10.5	10.8	11.3	11.7	12.3	12.6	11.5	11.7	11.3	0.6
41	F.S	409611	47	MALE	56	20.3	YES	NO	CGN	28	1.53	9.2	8.9	8.6	9.2	9.5	10.2	10.5	10.3	10.6	10.5	11.5	11.2	11.2	0.6
42	Y.S	1215664	64	MALE	80	24.3	YES	YES	CAD	18	1.57	8.4	8.6	8.5	8.9	9.2	9.8	10.5	10.9	11.2	11.8	12.3	11.9	11.6	0.6
43	U.S	1231470	57	MALE	84	24.5	YES	YES		36	1.48	8.4	7.8	8	8.5	9.1	9.6	10.2	9.6	11.3	11.6	10.8	10.6	10.8	0.6
44	B.K	1108856	68	MALE	64	16.8	YES	YES		41	1.32	8.9	8.5	8.6	8.9	9.2	9.4	9.3	9.5	9.6	NA	NA	NA	NA	0.6
45	I.S	660167	55	MALE	67	23.2	YES	YES		28	1.49	8.2	7.8	7.1	8	7.9	8.1	8.5	9.1	9.3	9.8	10.1	10.3	10.4	0.6
46	D.D	1169966	59	FEMALE	63	25.2	YES	YES		22	1.28	8.2	7.7	8.1	8.6	8.8	9.5	9.1	9.3	9.6	10.1	9.8	9.7	10.2	0.6
47	A.S	1238050	44	FEMALE	60	21.3	YES	NO	CGN	18	1.29	8.6	8.3	7.8	8.2	8.9	9.3	9.9	10.2	10.3	10.4	11.5	12	12.6	0.6
48	U.R	1222669	55	FEMALE	50	20.6	YES	NO	CIN	24	1.43	8.5	8.8	9.2	9.4	9.8	10.1	10.5	11.1	11	11.6	11.2	10.9	11.2	0.6
49	G.S	1243717	57	MALE	68	23.6	YES	YES	CGN	12	1.58	8.7	8.3	8.1	8.7	9.3	9.5	9.6	10.2	10.1	11	10.8	11.2	11.3	0.6
50	B.K	651593	58	MALE	54	16.8	YES	YES		30	1.19	9.4	9.3	9.5	9.9	7	NA	NA	NA	NA	NA	NA	NA	NA	0.6

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SR. No.	PATIENT INITIALS	MRD No	ERYTHROPOETIN DOSE (IU/KG)/ (mcg/KG)						blood transfusion (y/n)	hb response (y/n)	time to hb response (week)	tsat(%) (week)					ferritin (week)					B12	FOLATE	CRP	ADVERSE EVENTS	DEATH
			4 week	8 week	12 week	16 week	20 week	24 week				0	6	12	18	24	0	6	12	18	24					
1	J.S	93483	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	12	27.3	30	34	41	40	560	380	489	510	500	890	7,9	4.3	HIGH BP	
2	R.S	860109	0.9	1.2	1.5	1.8	1.8	1.8	YES	NO	NA	41	20.6	28.4	28.8	34.4	700	570	384	406	458	2009	7.9	6.2		
3	M.S	921456	0.9	1.2	1.5	1.8	1.9	2.1	NO	NO	NA	36.5	26.8	30.3	32.8	46.5	561	440	340	510	548	>2000	10.6	8	HIGH BP	
4	H.L	945467	0.75	0.9	0.9	0.9	0.9	0.9	NO	YES	10	31.6	36	24	28.5	37	526	496	536	610	582	>2000	8.9	0.2		
5	D.S	154306	0.9	1.2	1.5	1.8	1.8	2.1	NO	NO	NA	32	34.5	37.6	42	35.7	910	1003	810	792	569	910	7.6	3.8	HIGH BP	
6	C.S	243503	0.75	0.75	0.75	0.75	0.75	0.75	NO	YES	8	35	41	47	49	51	701	554	380	484	424	>2000	10.8	2.2		
7	G.S	1006804	0.75	0.75	0.75	0.75	0.75	0.75	NO	YES	6	37.7	42.6	31.4	34.3	40	583	610	482	510	593	>1000	5.6	2.3		
8	L.K	419328	0.75	0.75	0.75	0.75	0.75	0.75	NO	YES	8	33.4	35.4	36.6	37.1	40.6	613	728	633	515	712	1280	7.5	5.3		
9	H.K	925412	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	16	23	30.9	31.6	31	28	546	658	630	582	710	>2000	6	0.1	HIGH BP	
10	K.R	716342	0.9	0.9	0.9	0.9	0.9	0.9	NO	YES	12	37.5	19	28	37	39	610	563	480	512	640	>1000	8.2	4.6		
11	M.L.C	317434	0.6	0.6	0.6	0.6	0.6	0.6	NO	YES	8	59	53	56	41.1	43	636	756	842	721	832	>2000	6.2	1.2	HIGH BP	
12	D.A	234168	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	10	51	39	37	38	51	638	721	542	621	638	1382	8.9	2.4		
13	K.K	34714	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	10	39.3	37.1	32.5	37.9	29.7	678	556	610	531	657	>2000	8.5	1.2		
14	R.V	942022	0.9	0.9	0.9	0.9	0.9	0.9	NO	YES	8	35	26	28	38	43	512	618	580	583	621	>1000	5.8	4.5		
15	S.K	93483	0.9	NA	NA	NA	NA	NA	NO	NA	NA	29.6	NA	NA	NA	NA	630	NA	NA	NA	NA	>2000	6	1.2	HIGH BP	YES-CARDIAC ARREST
16	R.S	667922	0.9	1.2	1.5	1.8	2.1	2.1	YES	NO	NA	31.6	21	35	40.8	41	456	560	630	746	765	1890	8.6	2.13	NEED FOR BT	
17	M.R	140640	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	10	52	37	32	31	33	610	511	521	549	536	>2000	13.4	2.3		
18	H.S	552121	0.9	1.2	1.5	1.8	2.1	2.4	YES	NO	NA	30	32	33	30.7	32.2	574	632	748	546	491	2000	6.8	6	HIGH BP	
19	D.K	341389	0.75	0.75	0.75	0.75	0.75	0.75	NO	YES	8	39.2	32	46.6	36	37.8	894	726	765	630	564	>2000	8.9	1.5		
20	G.S	137314	0.9	1.05	1.2	1.2	1.2	1.2	NO	YES	12	40.4	49.8	46	34.4	37.1	750	680	632	541	498	>2000	6.8	3.2		
21	K.K	494453	0.9	1.05	1.2	1.2	1.2	1.2	NO	YES	12	33	28	47.3	47	34.8	512	428	610	632	730	>2000	8.6	2.8		
22	R.G	1217297	0.75	0.75	0.75	0.75	0.75	0.75	NO	YES	8	52.5	37.5	33.8	47.8	41.7	464	480	496	524	544	>2000	16.1	2.1		
23	M.S	70714	0.75	0.9	1.05	1.05	1.05	1.05	NO	YES	10	35	33	66	46	48	511	536	540	480	512	>1000	10.8	5.2		
24	H.S	900038	0.9	1.2	1.2	1.2	1.2	1.2	NO	YES	10	57	49	43	47	42	810	623	733	521	683	>2000	8.9	1.2		
25	K.B	469758	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	12	38.4	28.4	56.9	51.3	45.9	560	479	398	469	532	1800	7.4	1.8		
26	V.K.G	375319	0.9	1.2	1.2	1.2	NA	NA	NO	YES	12	27.3	30	34	41	NA	560	380	489	510	NA	890	7.9	4.3	HIGH BP	YES
27	S.K	974111	0.9	1.2	1.5	1.5	1.5	1.5	YES	YES	20	41	20.6	28.4	28.8	34.4	700	570	384	406	458	2009	7.9	6.2		
28	B.K	249918	0.75	0.9	0.9	0.9	0.9	0.9	NO	YES	12	55.6	50.7	55.6	43.7	46.5	761	560	340	480	420	>2000	10.6	2.1	HIGH BP	
29	G.J	989542	0.75	0.75	0.75	0.75	0.75	0.75	NO	YES	8	39.2	32	46.6	36	37.8	894	726	765	630	564	>2000	8.9	1.5		
30	B.K	52239	0.9	1.05	1.2	1.2	1.2	1.2	NO	YES	12	40.4	49.8	46	34.4	37.1	750	680	632	541	498	>2000	6.8	3.2		
31	J.S	1195868	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	12	33	28	47.3	47	34.8	512	428	610	632	730	>2000	8.6	2.8		
32	H.S	626595	0.75	0.75	0.75	0.75	0.75	0.75	NO	YES	8	52.5	37.5	33.8	47.8	41.7	464	480	496	524	544	>2000	16.1	2.1		
33	A.K	1010678	0.75	0.9	1.2	1.2	1.2	1.2	NO	YES	10	35	33	66	46	48	511	536	540	480	512	>1000	10.8	5.2		
34	A.S	1030379	0.9	0.9	0.9	0.9	0.9	0.9	NO	YES	8	32	34.5	37.6	42	35.7	910	1003	810	792	569	910	7.6	3.8	HIGH BP	
35	C.L	1244466	0.75	0.9	0.9	0.9	0.9	0.9	NO	YES	8	35	41	47	49	51	701	554	380	484	424	>2000	10.8	2.2		
36	T.C	1203171	0.9	1.2	1.5	1.8	2.1	2.4	NO	NO	NA	37.7	30.3	26	34.3	25.7	583	610	482	510	593	>1000	5.6	2.3		
37	A.D	120405	0.75	0.75	0.75	0.75	0.75	0.75	NO	YES	8	33.4	35.4	36.6	37.1	40.6	613	728	633	515	712	1280	7.5	5.3		
38	G.K	667408	0.9	1.2	1.2	1.2	1.2	1.2	NO	YES	16	23	30.9	31.6	31	28	546	658	630	582	710	>2000	6	0.1	HIGH BP	
39	A.C	266575	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	12	37.5	19	28	37	39	610	563	480	512	640	>1000	8.2	4.6		
40	D.P.G	1017709	0.6	0.6	0.6	0.6	0.6	0.6	NO	YES	8	59	53	56	41.1	43	636	756	842	721	832	>2000	6.2	1.2	HIGH BP	
41	F.S	409611	0.9	1.05	1.2	1.2	1.2	1.2	NO	YES	10	51	39	37	38	51	638	721	542	621	638	1382	8.9	2.4		
42	Y.S	1215664	0.75	0.9	0.9	0.9	0.9	0.9	NO	YES	10	39.3	37.1	32.5	37.9	29.7	678	556	610	531	657	>2000	8.5	1.2		
43	U.S	1231470	0.9	0.9	0.9	0.9	0.9	0.9	NO	YES	8	35	26	28	38	43	512	618	580	583	621	>1000	5.8	4.5		
44	B.K	1108856	0.9	1.05	1.2	1.5	NA	NA	NO	NA	NA	29.6	21	31	NA	NA	630	800	980	NA	NA	>2000	6	1.2	DEATH DUE TO CARDIAC ARREST	YES
45	I.S	660167	0.9	1.2	1.35	1.5	1.5	1.5	YES	YES	18	31.6	21	35	40.8	42	456	560	630	746	765	1890	8.6	2.13	NEED FOR BT	
46	D.D	1169966	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	10	52	37	32	31	33	610	511	521	549	536	>2000	13.4	2.3		
47	A.S	1238050	0.9	1.05	1.2	1.2	1.2	1.2	NO	YES	12	30	32	33	30.7	32.2	574	632	748	546	491	2000	6.8	6	HIGH BP	
48	U.R	1222669	0.75	0.75	0.75	0.75	0.75	0.75	NO	YES	8	39.2	32	46.6	36	37.8	894	726	765	630	564	>2000	8.9	1.5		
49	G.S	1243717	0.9	1.05	1.05	1.05	1.05	1.05	NO	YES	12	40.4	49.8	46	34.4	37.1	750	680	632	541	498	>2000	6.8	3.2		
50	B.K	651593	0.75	1.05	NA	NA	NA	NA	NO	NA	NA	29.6	21	NA	NA	NA	630	800	NA	NA	NA	>2000	6	1.2	DEATH DUE TO IC BLEED	YES

SR. No.	PATIENT INITIALS	MRD No	EPO Group
1	J.S	93483	CERA Group
2	R.S	860109	
3	M.S	921456	
4	H.L	945467	
5	D.S	154306	
6	C.S	243503	
7	G.S	1006804	
8	L.K	419328	
9	H.K	925412	
10	K.R	716342	
11	M.L.C	317434	
12	D.A	234168	
13	K.K	34714	
14	R.V	942022	
15	S.K	93483	
16	R.S	667922	
17	M.R	140640	
18	H.S	552121	
19	D.K	341389	
20	G.S	137314	
21	K.K	494453	
22	R.G	1217297	
23	M.S	70714	
24	H.S	900038	
25	K.B	469758	
26	V.K.G	375319	
27	S.K	974111	
28	B.K	249918	
29	G.J	989542	
30	B.K	52239	
31	J.S	1195868	
32	H.S	626595	
33	A.K	1010678	
34	A.S	1030379	
35	C.L	1244466	
36	T.C	1203171	
37	A.D	120405	
38	G.K	667408	
39	A.C	266575	
40	D.P.G	1017709	
41	F.S	409611	
42	Y.S	1215664	
43	U.S	1231470	
44	B.K	1108856	
45	I.S	660167	
46	D.D	1169966	
47	A.S	1238050	
48	U.R	1222669	
49	G.S	1243717	
50	B.K	651593	

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Date 2/3/2021

The Principal,
DMC, Ludhiana

Subject: Approval of Plan of Thesis

This is to inform you that the Faculty of Medical Sciences in its meeting held on 22.01.2021 has approved the plan of thesis of Dr Rohan, a student of your college for DM Nephrology along with the names of Supervisor/Co-Supervisor as under:-

Topic Plan of Thesis
Comparative efficacy of continuous erythropoietin receptor activator vs conventional epo therapy in correcting anemia in patients on long-term hemodialysis

Supervisor
Dr. Preet Mohinder Singh
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Co-Supervisor
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Prof.,

The student has to submit the three copies of thesis (along with PDF format) , to the Controller of Examinations, BFUHS, Faridkot, at least six months before the commencement of theory examination, if he/she is otherwise eligible to take the examination. He /She must directed to attach a photocopy of this letter with the forwarding letter while submitting thesis to the University along with the letter of approval of University for change of supervisor/Co-Supervisor, change of topic,(if any).

Dr. S P Singh MS(Oph)
Controller of Examinations

Note :

10. *If any discrepancy found regarding topic of thesis or Supervisor/Co-Supervisor, inform undersigned within one month after issue of this letter.*

COMPARATIVE EFFICACY OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR VS CONVENTIONAL EPO THERAPY IN CORRECTING ANEMIA IN PATIENTS ON LONG-TERM HEMODIALYSIS

THESIS PROPOSAL

FOR APPROVAL OF SUBJECT OF THESIS TO BE SUBMITTED

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTORATE OF MEDICINE

IN

NEPHROLOGY

OF THE

BABA FARID UNIVERSITY OF HEALTH SCIENCES
FARIDKOT

FEBRUARY, 2020

DR. ROHAN

DEPARTMENT OF NEPHROLOGY
DAYANAND MEDICAL COLLEGE & HOSPITAL
LUDHIANA

ABSTRACT OF PLAN OF THESIS

Title	COMPARATIVE EFFICACY OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR VS CONVENTIONAL EPO THERAPY IN CORRECTING ANEMIA IN PATIENTS ON LONG-TERM HEMODIALYSIS
For the degree of	D.M Nephrology
Name of the candidate	Dr. Rohan
Supervisor	Dr. Preet Mohinder Singh, Assistant. Professor Department of Nephrology, DMCH, Ludhiana
Co-supervisor	Dr. Suman Sethi, Assistant. Professor, Department of Nephrology, DMCH, Ludhiana Dr. Bhavna Garg ,Professor, Department of Pathology, DMCH, Ludhiana
Institution	Dayanand Medical College & Hospital, Ludhiana
University	Baba Farid University of Health Sciences, Faridkot

Introduction: Most patients with chronic kidney disease (CKD) develop anemia along with progressive loss of renal function. Anemia is caused by a relative deficiency of erythropoietin (EPO). The short half-lives of traditional ESAs may contribute to considerable fluctuations in haemoglobin (Hb) levels beyond target ranges, which is seen often in patients with CKD treated with these agents. Therefore, EPO with extended half-life and sustained efficacy may improve the convenience and therapeutic utility of the drug. Continuous erythropoietin receptor activator (CERA) is composed of epoetin beta chemically bound to a linear methoxy-polyethylene glycol moiety hence has an increased half life. This study will be conducted to demonstrate the efficacy of CERA treatment for correction of anemia in Indian patients receiving dialysis

Aim of Study: To compare the efficacy of IV CERA versus conventional IV epoetin beta in correcting anemia in Indian population on maintenance hemodialysis support.

Materials & methods: This is an Open-label, single center, randomized, parallel-group. The Study is of 24 weeks duration (excluding the screening period). After a 2-week screening period, a total of 100 eligible patients will be randomized 1:1 in two groups to receive either CERA or epoetin beta. During 24-week study period, dose adjustments will be performed to achieve Hb level≥11 g/dL and an increase of ≥1 g/dL from each patient's baseline Hb. CERA doses will be adjusted accord¬ing to the predefined protocol, but no more often than once ev¬ery 4 weeks. Patients will be evaluated weekly during the screening and every 2 weeks during the 24 weeks study period ,and at the final visit. For all patients who will receive at least one dose of study drug, adverse events (AEs) will be recorded.

Clinical Significance: To compare the efficacy of IV CERA versus conventional IV epoetin beta in correcting anemia in Indian population on maintenance hemodialysis support.

Keywords: EPO, CERA, CKD

(Signature) Candidate	(Signature) Co-supervisor	(Signature) Co-supervisor	(Signature) Supervisor	(Signature) Principal

CERTIFICATE OF FACILITIES AVAILABLE

This is to certify that the facilities for work on the subject of thesis titled **"COMPARATIVE EFFICACY OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR VS CONVENTIONAL EPO THERAPY IN CORRECTING ANEMIA IN PATIENTS ON LONG-TERM HEMODIALYSIS"** exist in the Department of Nephrology, DMC&H, Ludhiana and will be provided to the candidate. We will see that the data being included in the thesis is genuine and is collected by the candidate himself under our supervision and guidance.

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APPROVAL PROFORMA
BYRESEARCH & ETHICAL COMMITTEE
DAYANAND MEDICAL COLLEGE & HOSPITAL, LUDHIANA

Name of candidate	Dr. Rohan
Department	Nephrology
Topic of Thesis	Comparative efficacy of Continuous Erythropoietin Receptor Activator vs conventional EPO therapy in correcting Anemia in Patients on Long-Term Hemodialysis
Likely date of appearing in PG examination	May, 2022
Date of enrollment	28st August 2019
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Signature of Members of Research Committee with Stamp	**Signature of Members of Ethics Committee with Stamp**
Dr. Jaspal Singh (Professor & Head, Surgery)	Mr. A K Jindal (Member, Ethics Committee)
Dr. Dinesh Gupta (Professor & Head, Medicine)	Dr. Anu Sharma (Professor, Anatomy)
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PROFORMA FOR REGISTRATION OF SUBJECT FOR DISSERTATION

1	NAME OF THE CANDIDATE AND ADDRESS	Dr. ROHAN
2	NAME OF THE INSTITUTE	Dayanand Medical College, Ludhiana.
3	COURSE OF STUDY AND SUBJECT	D.M., Nephrology
4	DATE OF ADMISSION OF COURSE	28st AUGUST 2019
5	TITLE OF THE TOPIC	Comparative efficacy of Continuous Erythropoietin Receptor Activator vs conventional EPO therapy in correcting Anemia in Patients on Long-Term Hemodialysis

6. BRIEF RESUME OF THE INTENDED WORK

6.1 NEED FOR THE STUDY

Most patients with chronic kidney disease (CKD) develop anemia along with progressive loss of renal function. Anemia is caused by a relative deficiency of erythropoietin (EPO). After recombinant human EPO was introduced in 1989, exogenous replacement of EPO became the standard treatment of anemia in patients with CKD.[1] In patients with CKD on dialysis, treatment of anemia requires life-long replacement with EPOs. Traditional ESAs have relatively short intravenous (IV) half-lives (epoetin alfa and beta, _7 to 9 hours[2]; darbepoietin alfa, _25 hours[3] and require frequent (up to 3 times weekly) administration.[4,5] The short half-lives of these ESAs also may contribute to considerable fluctuations in haemoglobin (Hb) levels beyond target ranges, which is seen often in patients with CKD treated with these agents.[6-10] Only around 40% of dialysis patients are within Hb level target range (11 to 12 g/dL [110 to 120 g/L]) at any time, and many move in and out of range over time.

Thus, maintaining stable Hb levels at greater than 11 g/dL (_110 g/L) requires regular monitoring and often involves frequent ESA dose adjustments, which is time consuming and labor intensive, a burden that is expected to increase with the predicted increase in CKD prevalence.[11-13]

One approach to address this challenge is the introduction of agents that produce smooth and steady erythropoiesis at extended administration intervals and will provide predictable responses across the entire CKD continuum without loss of Hb level stability. Therefore, EPO with extended half-life and sustained efficacy may improve the convenience and therapeutic utility of the drug.

Continuous erythropoietin receptor activator (CERA) is composed of epoetin beta chemically bound to a linear methoxy-polyethylene glycol moiety.[14] In contrast with short-acting EPOs, CERA shows an increased half life, about 130 hr.[15] The ability to use CERA and conventional EPOs, with correction or maintenance purposes has been examined in six phase III clinical trials.[16-21] Among them, there was

one phase III correction study which showed comparable efficacy with once every 2 weeks intravenous (IV) administration of CERA to that of 3 times weekly epoetin for hemoglobin (Hb) correction in EPO-naïve patients on dialysis.[16] As this trial contained the patients on the relatively short-term dialysis and small number of Asian patients (less than 10%), there is a lack of evidence of efficacy and safety in general dialysis patients and also in Indian patient population.

This study will be conducted to demonstrate the efficacy of CERA treatment for correction of anemia in Indian patients receiving dialysis.

6.2 REVIEW OF LITERATURE

Anemia is an almost universal complication of chronic kidney disease (CKD). It contributes considerably to reduced quality of life of patients with CKD and has been associated with a number of adverse clinical outcomes. Before the availability of recombinant human erythropoietin (rHuEPO, or epoetin), patients on dialysis frequently required blood transfusions, exposing them to the risks of iron overload, transmission of viral hepatitis, and human leukocyte antigen (HLA) sensitization, which reduced the chances of successful transplantation.

The advent of rHuEPO in the late 1980s changed this situation completely. There is a strong rationale for managing anemia in CKD patients, and yet the optimal treatment strategies are still incompletely defined. Apart from therapy with erythropoiesis-stimulating agents (ESAs), iron replacement is essential for anemia management.

PATHOGENESIS

Renal anemia is typically an isolated normochromic, normocytic anemia with no leukopenia or thrombocytopenia. Both RBC life span and the rate of RBC production are reduced, but the latter is more important. The normal bone marrow has considerable capacity to increase the rate of erythropoiesis, and compensation normally could be easily made for the reduction in erythrocyte life observed in association with CKD. However, this EPO-induced compensatory increase in erythrocyte production is impaired in CKD.

Erythropoetin is normally produced by interstitial fibroblasts in the renal cortex, in close proximity to tubular epithelial cells and peritubular capillaries. In addition, hepatocytes and perisinusoidal, or Ito, cells in the liver can produce EPO. Hepatic EPO production dominates during fetal and early postnatal life but does not compensate for the loss of renal production in adult organisms.

Subtle changes in blood oxygen content induced by anemia, reduced environmental oxygen concentrations, and high altitude stimulate the secretion of EPO through a widespread system of oxygen-dependent gene expression. Central to this process is a family of hypoxia-inducible transcription factors (HIFs).

The two most important members of this family, HIF-1 and HIF-2, are composed of an oxygen-regulated a subunit (HIF-1a or HIF-2a) and a constitutive b subunit. The production of HIF-1a and HIF-2a is largely independent of oxygen, but their degradation is related to cellular oxygen concentrations. Hydroxylation of specific prolyl and asparagyl residues of HIF-a, for which molecular oxygen is required as a substrate, determines proteasomal destruction of HIF and inhibits its transcriptional activity. Apart from EPO, several hundred HIF target genes have been identified. HIF-2, rather than HIF-1, is the transcription factor primarily responsible for the regulation of EPO production.

The production capacity for EPO remains significant, even in end-stage renal disease. Thus patients with anemia and CKD can respond with a significant increase in EPO production to an additional hypoxic stimulus. The main problem therefore appears to be a failure of EPO production to increase in response to chronically reduced hemoglobin (Hb) concentrations.

EPO is a glycoprotein hormone consisting of a 165–amino acid protein backbone and four complex, heavily sialylated carbohydrate chains. The latter are essential for the biologic activity of EPO in vivo because partially or completely deglycosylated EPO is rapidly cleared from the circulation. This is why rHuEPO has to be manufactured in mammalian cells; bacteria lack the capacity to glycosylate recombinant proteins.

EPO stimulates RBC production by binding to homodimeric EPO receptors, which are primarily located on early erythroid progenitor cells, the burst-forming units erythroid (BFU-e) and the colony-forming units erythroid (CFU-e). Binding of EPO to its receptors salvages these progenitor cells and the subsequent earliest erythroblast generation from apoptosis, thereby permitting cell division and maturation into RBCs. Inhibition of RBC production by yet unknown uremic inhibitors of erythropoiesis may contribute to the pathogenesis of renal anemia, and dialysis per se can improve renal anemia and the efficacy of ESAs. An alternative view to the accumulation of inhibitors of erythropoiesis in CKD is that in many patients there is overlap between renal anemia

and the anemia of chronic disease, which is characterized by inhibition of EPO production and EPO efficacy, as well as by reduced iron availability, mediated through inflammatory cytokines. The hepatic release of hepcidin, the key regulator of iron metabolism, is upregulated in states of inflammation; it simultaneously blocks iron absorption from the gut and promotes iron sequestration in macrophages.

Epoetin Therapy

Manufacture of rHuEPO is achieved by gene transfer into a suitable mammalian cell line such as Chinese hamster ovary (CHO) cells. Like the endogenous hormone, rHuEPO consists of a 165–amino acid backbone with one *O*-linked and three *N*-linked glycosylation chains. The EPOs are administered either intravenously or subcutaneously. The earliest clinical trials of EPO used intravenous injections two or three times per week. This was partly because of the short half-life of EPO (6 to 8 hours after intravenous administration) and partly because of the convenience for the patient on dialysis. Although the bioavailability of subcutaneous EPO is 20% to 30%, the prolonged half-life after subcutaneous administration compared with intravenous administration allows less frequent injections. Furthermore, the dose required to achieve the same Hb response is about 30% lower with subcutaneous than with intravenous administration. There appears to be little difference in efficacy among the thigh, arm, or abdomen as injection sites.

Methoxypolyethylene Glycol Epoetin Beta

Alternative bioengineering techniques to prolong the half-life of EPO further have resulted in the development of methoxypolyethylene glycol epoetin beta (also called "continuous erythropoietin receptor activator" [CERA]), a PEGylated derivative of epoetin beta with an elimination half-life of about 130 hours when administered IV or SC. A methoxypolyethylene glycol polymer chain is integrated through amide bonds between the N-terminal amino group or the ε-amino group of lysine (predominantly lysine-52 or lysine-45), with a single succinimidyl butanoic acid linker. The molecular weight of CERA is twice that of

epoetin (~60 kDa). Phase III studies have shown that because of the longer half-life time of CERA, less frequent injections are sufficient to maintain stable hemoglobin values CERA given IV once every 2 weeks was found to be as safe and effective as epoetin given thrice weekly for correcting anemia in patients on hemodialysis.[16] A larger study has also shown that CERA given at 4-week dosing intervals was not inferior to CERA given once in 2 weeks in terms of maintaining Hbg concentrations when compared to thrice weekly administration of conventional epo. A total of 673 patients were randomized to receive either CERA (once in 2 weeks/ once in 4 weeks) and thrice weekly conventional epo. The mean change from baseline haemoglobin for patients who had switched to intravenous methoxy polyethylene glycol-epoetin beta every 2 weeks (-0.71 g/L, 95% CI -2.20 to 0.77) or every 4 weeks (-0.25 g/L, -1.79 to 1.29) was non-inferior to the mean change for patients who continued treatment with epoetin (-0.75 g/L, -2.26 to 0.75) ($p<0.0001$ for both comparisons). Of the 666 patients who received at least one dose of study drug, the incidence of adverse events or serious adverse events did not differ between groups ($p=0.30$ and $p=0.40$, respectively).[18]

In a Conchrane database review, 27 studies involving 5410 adults with CKD were included. Seven studies (1273 participants) involved people not requiring dialysis, 19 studies (4209 participants) involved people treated with dialysis and one study (71 participants) evaluated treatment in recipients of a kidney transplant. Treatment was given for 24 weeks on average. One study compared CERA with placebo, nine studies CERA with epoetin alfa or beta, nine studies CERA with darbepoetin alfa, and two studies compared CERA with epoetin alfa or beta and darbepoetin alfa. Three studies assessed the effects of differing frequencies of CERA administration and five assessed differing CERA doses. There was low certainty evidence that CERA had little or no effects on mortality (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65), major adverse cardiovascular events (RR 5.09, 95% CI 0.25 to 105.23; RR 5.56, 95% CI 0.99 to 31.30), hypertension (RR 1.01, 95% CI 0.75 to 1.37; RR 1.00, 95% CI 0.79 to

1.28), need for blood transfusion (RR 1.02, 95% CI 0.72 to 1.46; RR 0.94, 95% CI 0.55 to 1.61), or additional iron therapy (RR 1.03, 95% CI 0.91 to 1.15; RR 0.99, 95% CI 0.95 to 1.03) compared to epoetin alfa/beta or darbepoetin alfa respectively.[22] So far, no significant differences in outcomes or complications have emerged for CERA compared with other ESAs.

In another prospective, open-labelled, pilot clinical study conducted in India, 35 adult type 2 diabetes patients with nephropathy and renal anaemia, who were not on dialysis nor receiving treatment with ESA were administered CERA subcutaneously once in two weeks for a period of 24 weeks. The primary efficacy end point in this study was to evaluate the Hb response (Hb rise of ≥1 g/dl above the baseline or Hb level ≥11 g/dl) during the study period. All patients showed Hb rise ≥1 g/dl during the study period and 80 per cent patients could achieve Hb value ≥11 g/dl. The maximum median Hb rise of 1.2 g/dl occurred in the initial 6 weeks after starting the treatment. The mean creatinine clearance (CrCl) improved by 2.8 ml/min, with mean Hb rise of 2.6 g/dl from the baseline after administration of CERA. Hence concluding that CERA once in two weeks was efficacious in correcting anaemia in the ESA-naïve patients with diabetic nephropathy who are not on dialysis.[23]

6.3 AIMS AND OBJECTIVES OF THE STUDY

To compare the efficacy of IV CERA versus conventional IV epoetin beta in correcting anemia in Indian population on maintenance hemodialysis support.

7. MATERIALS AND METHODS

Study will be conducted in patients undergoing maintenance hemodialysis at DMCH Dialysis centre from May 2020– May 2021. The study population will be followed up for duration of the study i.e 24 weeks (till Oct 2021)

Study Design:

Open-label, single center, randomized, parallel-group study

Source of Data

The study population will be enrolled from patients undergoing maintenance hemodialysis in DMCH Dialysis centre from the period of May 2020 to May 2021.

Methods of collection of Data

After an informed consent, enrolled patients in this study will be subjected to relevant history taking, physical examination and investigations (details attached with proforma). A predefined and well-structured proforma will be used to collect the whole data.

BASELINE INVESTIGATIONS

Complete Hemogram, including Peripheral blood film
Serum creatinine, urea & serum Na/K
Serum iron
TIBC
Serum Ferritin
Reticulocyte count
Serum B12
Serum folate
Serum CRP quantitative
anti-EPO antibody (wherever indicated)
ECG
2D Echo
Kt/v

TREATMENT PROTOCOL

The Study is of 24 weeks duration (excluding the screening period). After a 2-week screening period, a total of 100 eligible patients will be randomized 1:1 in two groups to receive either CERA or epoetin. The

starting dose is 0.6 μg/kg of CERA IV once every 2 weeks. The starting dose of epoetin is 40 IU/kg IV, three times per week. During 24-week study period, dose adjustments will be performed to achieve Hb level≥11 g/dL and an increase of ≥1 g/dL from each patient's baseline Hb. CERA doses will be adjusted according to the predefined protocol, but no more often than once every 4 weeks.

The predefined protocol is as follows;

1) if the Hb increased by <1 g/dL during 4 weeks compared with baseline, doses will be increased by 25%;

2) if Hb increased by >2 g/dL versus baseline or was between 12 g/dL and 13 g/dL, doses will be decreased by 25%;

3) if Hb was greater than 13 g/dL, then CERA to be stopped temporarily until Hb level decreased to less than 12 g/dL, then therapy will be resumed at a dose 25% below the previously administered dose;

4) if Hb decreased to less than baseline value and was less than 9 g/dL, doses will be increased by 50%.

Dose adjustments of conventional epoetin will be performed according to each investigator's discretion, but not more often than once every 4 weeks.

100mg IV iron supplementation will be prescribed once weekly to prevent iron deficiency during treatment period. Additional supplementation will be done if need be to maintain iron indices (serum ferritin≥500 ng/mL or transferrin saturation (TSAT)≥30% .

Assessment

Patients will be evaluated weekly during the screening and every 2 weeks during the 24 weeks study period, and at the final visit. Hemoglobin, hematocrit, blood pressure and heart rate will be measured at every visit. Iron and other safety laboratory parameters will be measured during screening, and every 6 weeks during the study and at the final visit.

For all patients who will receive at least one dose of study drug, adverse events (AEs) will be recorded. RBC transfusions, iron

supplementation, and concomitant medications will also be recorded throughout the study.

Primary End point

The primary efficacy parameter will be Hb response rate in the intention-to-treat (ITT) population. Hb response will be defined as increase of Hb by at least 1 g/dL compared with baseline and Hb≥11 g/dL without red blood cell (RBC) transfusion during 24-week correction period.

Secondary end points

Secondary efficacy parameters are;

1) mean hemoglobin levels and their changes over time from baseline,

2) time to Hb response, and

3) RBC transfusion rate during 24-week correction period.

INCLUSION CRITERIA:

1. Patients (age≥18 yr) receiving regular minimum twice weekly dialysis at least for 4 weeks before randomization.
2. Patients should be on adequate dialysis, that is, measured Kt/V ≥1.2 or urea reduction ratio (URR) ≥65% for hemodialysis (HD).
3. We defined baseline predialysis hemoglobin as mean of all values recorded between the day of first study dose and the previous 20 days. It must be between 8 and 11 g/dL.
4. Patients were also required to have adequate iron status, defined as serum ferritin≥500 ng/mL or transferrin saturation (TSAT)≥30%.

EXCLUSION CRITERIA:

1. New York Heart Association class III or IV congestive heart failure
2. Uncontrolled hypertension (defined as predialysis diastolic blood pressure [BP] ≥105 mmHg or systolic BP ≥160 mmHg during the screening period)
3. Evidence of uncontrolled hyperparathyroidism (defined as parathyroid hormone level >1000 pg/mL with no response to conventional treatment of hyperparathyroidism according to KDOQI guideline during the 12 months prior to baseline)
4. Treatment for Generalised Tonic Clonic Seizure

5. Hematological, inflammatory, or infectious conditions that might interfere with the erythropoietin response

6. Received red blood cell transfusions within 12 weeks before screening or during the screening/ baseline period

7. C-reactive protein >30 mg/L

8. The likelihood of early withdrawal or life expectancy of <12 months

9. Poor compliance with dialysis treatment, evidenced by more than two missed treatment monthly over the previous 3 months

10. Refuse to be involved in the study

STATISTICAL ANALYSIS

Data will be described in terms of range; mean ±standard deviation (± SD), median, frequencies (number of cases) and relative frequencies (percentages) as appropriate. Comparison of quantitative variables between the study groups will be done using Student t-test and Mann Whitney U test for independent samples for parametric and non-parametric data respectively. For comparing categorical data, Chi square ($\chi 2$) test will be performed and exact test will be used when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations will be done using SPSS (Statistical Package for the Social Science) SPSS 21 version statistical program for Microsoft Windows

SAMPLE SIZE CALCULATION

A post hoc power analysis was conducted using the software package, G*Power (Faul and Erdfelder 1992).The alpha level used for this analysis was $p<0.05$ and beta was 0.20. Sample size was estimated from the results of previous study[24] using the Hemoglobin response rate as the parameter, which is the primary outcome of our study. Our sample size came out to be 50 subjects per group at power of 0.80 and with an effect size of 0.28 with 10% chance of error with $\alpha = 0.05$, $\beta = 0.20$ and confidence interval of 95%.

7.3 DOES THE STUDY REQUIRE ANY INVESTIGATIONS OR INTERVENTIONS TO BE CONDUCTED ON PATIENTS OR OTHER HUMANS OR ANIMALS? IF SO, PLEASE DESCRIBE BRIEFLY.

Yes. Patients included in the study will have to undergo hematological, biochemical or radiological investigations and renal biopsy as per the protocol. For this patients included in the study will be informed regarding their inclusion and written informed consent will be taken for all the patients included in the study.

7.4 HAS ETHICAL CLEARENCE BEEN OBTAINED FROM YOUR INSTITUTION IN CASE OF 7.3?

YES

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PROFORMA

Sr. No.

Name Age/Sex Cr No.

Indoor/outdoor patient

Father/ Husband Name

Address

Phone No.

Date of enrollment

Diagnosis

Duration since diagnosis

Comorbidities

Chief Complaints

Past History

Family History

Personal History

Dietary habits

Bladder/ bowel

Smoking

Duration

Number of Pack Year

Signature of Candidate

Signature of Supervisor

Menstrual history

Treatment history

Medications

Compliance to treatment

General Physical Examination

Weight	Height	BMI
Blood Pressure	Pulse	Temperature
Pallor	Icterus	Clubbing
Cyanosis	Jugular venous Pressure	Lymphadenopathy

Dermatological examination

Signature of Candidate

Signature of Supervisor

Systemic Examination

Chest

CVS

P/A

CNS

Signature of Candidate

Signature of Supervisor

BLOOD INVES-TIGATIONS	WEEK 0	WEEK 2	WEEK 4	WEEK 6	WEEK 8	WEEK 10	WEEK 12	WEEK 14	WEEK 16	WEEK 18	WEEK 20	WEEK 22	WEEK 24
TLC													
Hb													
PC													
MCV													

Signature of Candidate

Signature of Supervisor

HEMATOCRIT													
s.Cr													
s. Urea													
s Na/K													
PBF													
SERUM IRON													
TIBC													

Signature of Candidate

Signature of Supervisor

SERUM FERRITIN													
Reticulocyte count													
SERUM B12													
SERUM FOLATE													
CRP QUANTITATIVE													
ANTI-EPO ANTIBODY (when indicated)													

Signature of Candidate

Signature of Supervisor

HEMATOCRIT													
s.Cr													
s. Urea													
s Na/K													
PBF													
SERUM IRON													
TIBC													

Signature of Candidate

Signature of Supervisor

Additional Investigations

ECG
2D Echo

NOTED ADVERSE EVENTS

Death

- Cardiovascular cause
- Sudden death
- Infections
- Others causes

Treatment Given	Date	Side-effects	Any special remarks

Signature of Candidate

Signature of Supervisor

INFORMED PATIENT CONSENT

Date: _____

I.....D/o, W/o, S/o.....
.....am willing to participate in the study **"COMPARATIVE EFFICACY OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR VS CONVENTIONAL EPO THERAPY IN CORRECTING ANEMIA IN PATIENTS ON LONG-TERM HEMODIALYSIS"**The procedure with its complications has been explained to me in local vernacular language. I have fully understood that no special tests and extra expenditure in any form, merely for the purpose of thesis is being carried out. I am free to opt out the study any time without assigning any reason.

.....
Signature of the Witness

Name:

.....
Signature of the patient

Signature of Candidate

Signature of Supervisor

मरीज अनुमति फार्म

तिथि _____

मैं _____ पत्नी/पुत्र/पुत्री _____

निवासी _____

इस शोधकार्य **"COMPARATIVE EFFICACY OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR VS CONVENTIONAL EPO THERAPY IN CORRECTING ANEMIA IN PATIENTS ON LONG-TERM HEMODIALYSIS"** में भाग लेने के लिए सहमत हूँ। मैं इस शोधकार्य में भाग लेने के लिए अपनी स्वेच्छा से तैयार हूँ। मैं पुष्टिम करता/करती हूँ की यह स्वीकृति देने के लिए मुझे कोई आर्थिक प्रलोभन नहीं दिया गया और न ही दबाव डाला गया है। मुझे इस शोधकार्य का उद्देअश्य स्पष्टदकर दिया गया है और मुझे यह विश्वाअस है की यह विज्ञान और मानवता के लाभ के लिए है। मुझे इस शोधकार्य में होने वाले जोखिम के बारे में समझा दिया गया है और मेरी समझ में यह जोखिम बहुत मामुली है।

मैं इस शोधकार्य में भाग लेने के सम्बन्ध में किसी भी समय अपनी अस्वीकृति व्यक्तमकर सकता /सकती हूँ और मेरे अस्वीकृति व्यक्तक करने का मेरे इलाज पर कोई प्रभाव नहीं पड़ेगा।

_____ _____

गवाह के हस्ताक्षर रोगी के हस्ताक्षर/अंगूठे का निशान

नाम: नाम:

_____

अन्वेषक केहस्ताक्षर

_____

विद्यार्थी के हस्ताक्षर

ਮਰੀਜ਼ ਰਜ਼ਾਮੰਦੀ ਫਾਰਮ

ਮਿਤੀ_____

ਮੈ_____ਪਤਨੀ/ਪੁੱਤਰ/ਪੁੱਤਰੀ_____

ਵਾਸੀ _____

COMPARATIVE EFFICACY OF CONTINUOUS ERYTHROPOIETIN RECEPTOR ACTIVATOR VS CONVENTIONAL EPO THERAPY IN CORRECTING ANEMIA IN PATIENTS ON LONG-TERM HEMODIALYSIS" ਤੇ ਚਲ ਰਹੀ ਖੋਜ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਰਜ਼ਾਮੰਦ ਹਾਂ। ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਲਈ ਮੈ ਆਪਣੀ ਮਰਜ਼ੀ ਨਾਲ ਤਿਆਰ ਹਾਂ। ਮੈ ਇਹ ਦਸਣਾ ਚਾਹੁੰਦਾ ਹਾਂ/ ਚਾਹੁੰਦੀ ਹਾਂ ਕੇ ਇਹ ਰਜ਼ਾਮੰਦੀ ਦੇਣ ਵਾਸਤੇ ਮੈਨੂ ਕਿਸੇ ਵੀ ਤਰਾਂ ਦਾ ਲੋਭ-ਲਾਲਚ ਨਹੀ ਦਿੱਤਾ ਗਿਆ ਅਤੇ ਨਾ ਹੀ ਕੋਈ ਦਬਾ ਪਾਇਆ ਗਿਆ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਦਾਮਨੇਰਥ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਭਰੋਸਾ ਦਵਾਇਆ ਗਿਆ ਹੈ ਕੇ ਇਹ ਖੋਜ ਵਿਗਿਆਨ ਅਤੇ ਮਾਨਵਤਾ ਦੀ ਭਲਾਈ ਲਈ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਵਿਚ ਹੋਣ ਵਾਲੇ ਖਤਰੇ ਬਾਰੇ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ ਅਤੇ ਮੈਨੂ ਇਹ ਯਕੀਨ ਹੈ ਕੇ ਇਹ ਖਤਰਾ ਬਹੁਤ ਮਾਮੂਲੀ ਹੈ। ਮੈਨੂ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਦਾ ਢੰਗ – ਤਰੀਕਾ ਸਮਝਾ ਦਿੱਤਾ ਗਿਆ ਹੈ।

ਮੈ ਇਸ ਖੋਜ ਕੰਮ ਵਿਚ ਹਿੱਸਾ ਲੈਣ ਬਾਰੇ ਆਪਣੀ ਰਜ਼ਾਮੰਦੀ ਕਿਸੇ ਵੀ ਸਮੇ ਵਾਪਸ ਲੈ ਸਕਦਾ ਹਾਂ/ ਸਕਦੀ ਹਾਂ ਅਤੇ ਮੇਰੀ ਰਜ਼ਾਮੰਦੀ ਵਾਪਸ ਲੈਣ ਦਾ ਮੇਰੇ ਇਲਾਜ ਤੇ ਕੋਈ ਅਸਰ ਨਹੀ ਹੋਵੇਗਾ।

_____
ਗਵਾਹਦੇਹਸਤਾਖਰ

_____
ਮਰੀਜ਼ਦੇਹਸਤਾਖਰ

ਮਿਤੀ_____

ਮਿਤੀ_____

ਪਤਾ _____

ਪਤਾ _____

_____
ਨਿਰੀਖਕਦੇ ਹਸਤਾਖਰ

_____
ਸਿਖਿਆਰਥੀ ਦੇ ਹਸਤਾਖਰ